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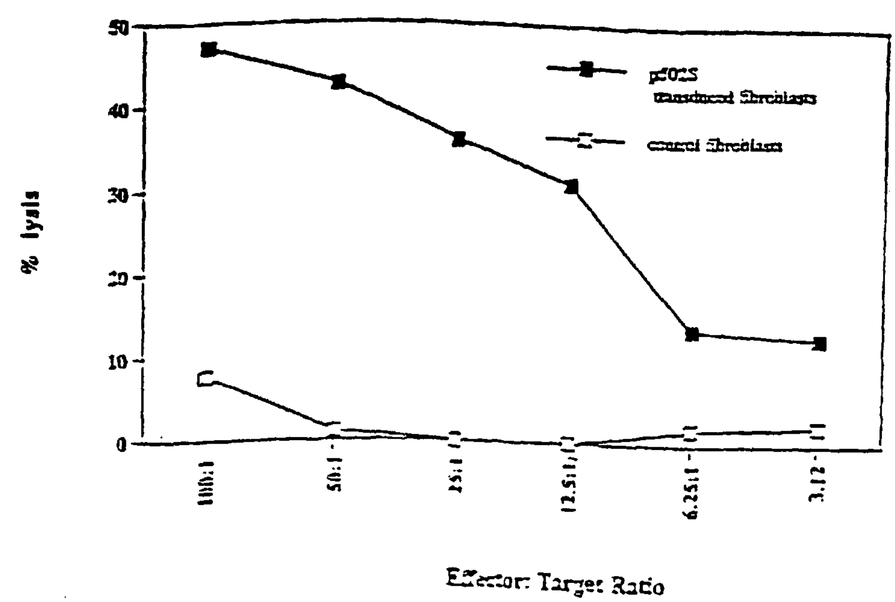
(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER



(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, particularly prostate cancer, are disclosed. Illustrative compositions comprise one or more prostate-specific polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly prostate cancer.

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COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides, comprising at least a portion of a prostate-specific protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides are useful in pharmaceutical compositions, *e.g.*, vaccines, and other compositions for the diagnosis and treatment of prostate cancer.

BACKGROUND OF THE INVENTION

Cancer is a significant health problem throughout the world. Although Cancer is a significant health problem throughout the world. Although advances have been made in detection and therapy of cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Current therapies, which are generally based on a combination of chemotherapy or surgery and radiation, continue to prove inadequate in many patients.

Prostate cancer is the most common form of cancer among males, with an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA)

and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides polynucleotide compositions comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(b) complements of the sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(d) sequences that hybridize to a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375,

381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, under moderately stringent conditions;

(e) sequences having at least 75% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(f) sequences having at least 90% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788; and

(g) degenerate variants of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

In one preferred embodiment, the polynucleotide compositions of the invention are expressed in at least about 20%, more preferably in at least about 30%, and most preferably in at least about 50% of prostate tissue samples tested, at a level that is at least about 2-fold, preferably at least about 5-fold, and most preferably at least about 10-fold higher than that for other normal tissues.

The present invention, in another aspect, provides polypeptide compositions comprising an amino acid sequence that is encoded by a polynucleotide sequence described above.

The present invention further provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383,

477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791.

In certain preferred embodiments, the polypeptides and/or polynucleotides of the present invention are immunogenic, *i.e.*, they are capable of eliciting an immune response, particularly a humoral and/or cellular immune response, as further described herein.

The present invention further provides fragments, variants and/or derivatives of the disclosed polypeptide and/or polynucleotide sequences, wherein the fragments, variants and/or derivatives preferably have a level of immunogenic activity of at least about 50%, preferably at least about 70% and more preferably at least about 90% of the level of immunogenic activity of a polypeptide sequence set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 or 789-791, or a polypeptide sequence encoded by a polynucleotide sequence set forth in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

The present invention further provides polynucleotides that encode a polypeptide described above, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, pharmaceutical compositions, *e.g.*, vaccine compositions, are provided for prophylactic or therapeutic applications. Such compositions generally comprise an immunogenic polypeptide or

polynucleotide of the invention and an immunostimulant, such as an adjuvant, together with a physiologically acceptable carrier.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a polypeptide of the present invention, or a fragment thereof; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Illustrative antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, pharmaceutical compositions are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins, typically in the form of pharmaceutical compositions, *e.g.*, vaccine compositions, comprising a physiologically acceptable carrier and/or an immunostimulant. The fusions proteins may comprise multiple immunogenic polypeptides or portions/variants thereof, as described herein, and may further comprise one or more polypeptide segments for facilitating and/or enhancing the expression, purification and/or immunogenicity of the polypeptide(s).

Within further aspects, the present invention provides methods for stimulating an immune response in a patient, preferably a T cell response in a human patient, comprising administering a pharmaceutical composition described herein. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or a patient considered to be at risk for such a disease may be treated prophylactically.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a

patient a pharmaceutical composition as recited above. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or a patient considered to be at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a polypeptide of the present invention, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the polypeptide from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a polypeptide of the present invention, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating $CD4^+$ and/or $CD8^+$ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of polypeptide disclosed herein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer, preferably a prostate cancer, in a patient comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b), and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide of the present invention; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide of the present invention, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to an inventive polynucleotide, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide of the present invention; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b), and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate-specific polypeptide P502S, as compared to control fibroblasts. The percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate-specific polypeptide P502S. In each case, the number of γ-interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to fibroblasts pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/*neu*.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release

bioassay. D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate-specific polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a $CD8^+$ cell line (3A-1) for a representative prostate-specific antigen (P501S). Figure 6A shows the results of a ^{51}Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferon-gamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target rations as indicated.

Figure 7 is a Western blot showing the expression of P501S in baculovirus.

Figure 8 illustrates the results of epitope mapping studies on P501S.

Figure 9 is a schematic representation of the P501S protein showing the location of transmembrane domains and predicted intracellular and extracellular domains.

Figure 10 is a genomic map showing the location of the prostate genes P775P, P704P, B305D, P712P and P774P within the Cat Eye Syndrome region of chromosome 22q11.2

Figure 11 shows the results of an ELISA assay to determine the specificity of rabbit polyclonal antisera raised against P501S.

SEQ ID NO: 1 is the determined cDNA sequence for F1-13

SEQ ID NO: 2 is the determined 3' cDNA sequence for F1-12

SEQ ID NO: 3 is the determined 5' cDNA sequence for F1-12

SEQ ID NO: 4 is the determined 3' cDNA sequence for F1-16

SEQ ID NO: 5 is the determined 3' cDNA sequence for H1-1

SEQ ID NO: 6 is the determined 3' cDNA sequence for H1-9

SEQ ID NO: 7 is the determined 3' cDNA sequence for H1-4

SEQ ID NO: 8 is the determined 3' cDNA sequence for J1-17

SEQ ID NO: 9 is the determined 5' cDNA sequence for J1-17

SEQ ID NO: 10 is the determined 3' cDNA sequence for L1-12

SEQ ID NO: 11 is the determined 5' cDNA sequence for L1-12

SEQ ID NO: 12 is the determined 3' cDNA sequence for N1-1862

SEQ ID NO: 13 is the determined 5' cDNA sequence for N1-1862

SEQ ID NO: 14 is the determined 3' cDNA sequence for J1-13

SEQ ID NO: 15 is the determined 5' cDNA sequence for J1-13

SEQ ID NO: 16 is the determined 3' cDNA sequence for J1-19

SEQ ID NO: 17 is the determined 5' cDNA sequence for J1-19

SEQ ID NO: 18 is the determined 3' cDNA sequence for J1-25

SEQ ID NO: 19 is the determined 5' cDNA sequence for J1-25

SEQ ID NO: 20 is the determined 5' cDNA sequence for J1-24

SEQ ID NO: 21 is the determined 3' cDNA sequence for J1-24

SEQ ID NO: 22 is the determined 5' cDNA sequence for K1-58

SEQ ID NO: 23 is the determined 3' cDNA sequence for K1-58

SEQ ID NO: 24 is the determined 5' cDNA sequence for K1-63

SEQ ID NO: 25 is the determined 3' cDNA sequence for K1-63

SEQ ID NO: 26 is the determined 5' cDNA sequence for L1-4

SEQ ID NO: 27 is the determined 3' cDNA sequence for L1-4

SEQ ID NO: 28 is the determined 5' cDNA sequence for L1-14

SEQ ID NO: 29 is the determined 3' cDNA sequence for L1-14

SEQ ID NO: 30 is the determined 3' cDNA sequence for J1-12

SEQ ID NO: 31 is the determined 3' cDNA sequence for J1-16

SEQ ID NO: 32 is the determined 3' cDNA sequence for J1-21

SEQ ID NO: 33 is the determined 3' cDNA sequence for K1-48

SEQ ID NO: 34 is the determined 3' cDNA sequence for K1-55
SEQ ID NO: 35 is the determined 3' cDNA sequence for L1-2
SEQ ID NO: 36 is the determined 3' cDNA sequence for L1-6
SEQ ID NO: 37 is the determined 3' cDNA sequence for N1-1858
SEQ ID NO: 38 is the determined 3' cDNA sequence for N1-1860
SEQ ID NO: 39 is the determined 3' cDNA sequence for N1-1861
SEQ ID NO: 40 is the determined 3' cDNA sequence for N1-1864
SEQ ID NO: 41 is the determined cDNA sequence for P5
SEQ ID NO: 42 is the determined cDNA sequence for P8
SEQ ID NO: 43 is the determined cDNA sequence for P9
SEQ ID NO: 44 is the determined cDNA sequence for P18
SEQ ID NO: 45 is the determined cDNA sequence for P20
SEQ ID NO: 46 is the determined cDNA sequence for P29
SEQ ID NO: 47 is the determined cDNA sequence for P30
SEQ ID NO: 48 is the determined cDNA sequence for P34
SEQ ID NO: 49 is the determined cDNA sequence for P36
SEQ ID NO: 50 is the determined cDNA sequence for P38
SEQ ID NO: 51 is the determined cDNA sequence for P39
SEQ ID NO: 52 is the determined cDNA sequence for P42
SEQ ID NO: 53 is the determined cDNA sequence for P47
SEQ ID NO: 54 is the determined cDNA sequence for P49
SEQ ID NO: 55 is the determined cDNA sequence for P50
SEQ ID NO: 56 is the determined cDNA sequence for P53
SEQ ID NO: 57 is the determined cDNA sequence for P55
SEQ ID NO: 58 is the determined cDNA sequence for P60
SEQ ID NO: 59 is the determined cDNA sequence for P64
SEQ ID NO: 60 is the determined cDNA sequence for P65
SEQ ID NO: 61 is the determined cDNA sequence for P73
SEQ ID NO: 62 is the determined cDNA sequence for P75
SEQ ID NO: 63 is the determined cDNA sequence for P76

SEQ ID NO: 64 is the determined cDNA sequence for P79

SEQ ID NO: 65 is the determined cDNA sequence for P84

SEQ ID NO: 66 is the determined cDNA sequence for P68

SEQ ID NO: 67 is the determined cDNA sequence for P80 (also referred to as P704P)

SEQ ID NO: 68 is the determined cDNA sequence for P82

SEQ ID NO: 69 is the determined cDNA sequence for U1-3064

SEQ ID NO: 70 is the determined cDNA sequence for U1-3065

SEQ ID NO: 71 is the determined cDNA sequence for V1-3692

SEQ ID NO: 72 is the determined cDNA sequence for 1A-3905

SEQ ID NO: 73 is the determined cDNA sequence for V1-3686

SEQ ID NO: 74 is the determined cDNA sequence for R1-2330

SEQ ID NO: 75 is the determined cDNA sequence for 1B-3976

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SEQ ID NO: 77 is the determined cDNA sequence for 1G-4736

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SEQ ID NO: 79 is the determined cDNA sequence for 1G-4741

SEQ ID NO: 80 is the determined cDNA sequence for 1G-4744

SEQ ID NO: 81 is the determined cDNA sequence for 1G-4734

SEQ ID NO: 82 is the determined cDNA sequence for 1H-4774

SEQ ID NO: 83 is the determined cDNA sequence for 1H-4781

SEQ ID NO: 84 is the determined cDNA sequence for 1H-4785

SEQ ID NO: 85 is the determined cDNA sequence for 1H-4787

SEQ ID NO: 86 is the determined cDNA sequence for 1H-4796

SEQ ID NO: 87 is the determined cDNA sequence for 1I-4807

SEQ ID NO: 88 is the determined cDNA sequence for 1I-4810

SEQ ID NO: 89 is the determined cDNA sequence for 1I-4811

SEQ ID NO: 90 is the determined cDNA sequence for 1J-4876

SEQ ID NO: 91 is the determined cDNA sequence for 1K-4884

SEQ ID NO: 92 is the determined cDNA sequence for 1K-4896

SEQ ID NO: 93 is the determined cDNA sequence for 1G-4761

SEQ ID NO: 94 is the determined cDNA sequence for 1G-4762

SEQ ID NO: 95 is the determined cDNA sequence for 1H-4766

SEQ ID NO: 96 is the determined cDNA sequence for 1H-4770

SEQ ID NO: 97 is the determined cDNA sequence for 1H-4771

SEQ ID NO: 98 is the determined cDNA sequence for 1H-4772

SEQ ID NO: 99 is the determined cDNA sequence for 1D-4297

SEQ ID NO: 100 is the determined cDNA sequence for 1D-4309

SEQ ID NO: 101 is the determined cDNA sequence for 1D.1-4278

SEQ ID NO: 102 is the determined cDNA sequence for 1D-4288

SEQ ID NO: 103 is the determined cDNA sequence for 1D-4283

SEQ ID NO: 104 is the determined cDNA sequence for 1D-4304

SEQ ID NO: 105 is the determined cDNA sequence for 1D-4296

SEQ ID NO: 106 is the determined cDNA sequence for 1D-4280

SEQ ID NO: 107 is the determined full length cDNA sequence for F1-12 (also referred to as P504S)

SEQ ID NO: 108 is the predicted amino acid sequence for F1-12

SEQ ID NO: 109 is the determined full length cDNA sequence for J1-17

SEQ ID NO: 110 is the determined full length cDNA sequence for L1-12 (also referred to as P501S)

SEQ ID NO: 111 is the determined full length cDNA sequence for N1-1862 (also referred to as P503S)

SEQ ID NO: 112 is the predicted amino acid sequence for J1-17

SEQ ID NO: 113 is the predicted amino acid sequence for L1-12 (also referred to as P501S)

SEQ ID NO: 114 is the predicted amino acid sequence for N1-1862 (also referred to as P503S)

SEQ ID NO: 115 is the determined cDNA sequence for P89

SEQ ID NO: 116 is the determined cDNA sequence for P90

SEQ ID NO: 117 is the determined cDNA sequence for P92

SEQ ID NO: 118 is the determined cDNA sequence for P95
SEQ ID NO: 119 is the determined cDNA sequence for P98
SEQ ID NO: 120 is the determined cDNA sequence for P102
SEQ ID NO: 121 is the determined cDNA sequence for P110
SEQ ID NO: 122 is the determined cDNA sequence for P111
SEQ ID NO: 123 is the determined cDNA sequence for P114
SEQ ID NO: 124 is the determined cDNA sequence for P115
SEQ ID NO: 125 is the determined cDNA sequence for P116
SEQ ID NO: 126 is the determined cDNA sequence for P124
SEQ ID NO: 127 is the determined cDNA sequence for P126
SEQ ID NO: 128 is the determined cDNA sequence for P130
SEQ ID NO: 129 is the determined cDNA sequence for P133
SEQ ID NO: 130 is the determined cDNA sequence for P138
SEQ ID NO: 131 is the determined cDNA sequence for P143
SEQ ID NO: 132 is the determined cDNA sequence for P151
SEQ ID NO: 133 is the determined cDNA sequence for P156
SEQ ID NO: 134 is the determined cDNA sequence for P157
SEQ ID NO: 135 is the determined cDNA sequence for P166
SEQ ID NO: 136 is the determined cDNA sequence for P176
SEQ ID NO: 137 is the determined cDNA sequence for P178
SEQ ID NO: 138 is the determined cDNA sequence for P179
SEQ ID NO: 139 is the determined cDNA sequence for P185
SEQ ID NO: 140 is the determined cDNA sequence for P192
SEQ ID NO: 141 is the determined cDNA sequence for P201
SEQ ID NO: 142 is the determined cDNA sequence for P204
SEQ ID NO: 143 is the determined cDNA sequence for P208
SEQ ID NO: 144 is the determined cDNA sequence for P211
SEQ ID NO: 145 is the determined cDNA sequence for P213
SEQ ID NO: 146 is the determined cDNA sequence for P219
SEQ ID NO: 147 is the determined cDNA sequence for P237

SEQ ID NO: 148 is the determined cDNA sequence for P239

SEQ ID NO: 149 is the determined cDNA sequence for P248

SEQ ID NO: 150 is the determined cDNA sequence for P251

SEQ ID NO: 151 is the determined cDNA sequence for P255

SEQ ID NO: 152 is the determined cDNA sequence for P256

SEQ ID NO: 153 is the determined cDNA sequence for P259

SEQ ID NO: 154 is the determined cDNA sequence for P260

SEQ ID NO: 155 is the determined cDNA sequence for P263

SEQ ID NO: 156 is the determined cDNA sequence for P264

SEQ ID NO: 157 is the determined cDNA sequence for P266

SEQ ID NO: 158 is the determined cDNA sequence for P270

SEQ ID NO: 159 is the determined cDNA sequence for P272

SEQ ID NO: 160 is the determined cDNA sequence for P278

SEQ ID NO: 161 is the determined cDNA sequence for P105

SEQ ID NO: 162 is the determined cDNA sequence for P107

SEQ ID NO: 163 is the determined cDNA sequence for P137

SEQ ID NO: 164 is the determined cDNA sequence for P194

SEQ ID NO: 165 is the determined cDNA sequence for P195

SEQ ID NO: 166 is the determined cDNA sequence for P196

SEQ ID NO: 167 is the determined cDNA sequence for P220

SEQ ID NO: 168 is the determined cDNA sequence for P234

SEQ ID NO: 169 is the determined cDNA sequence for P235

SEQ ID NO: 170 is the determined cDNA sequence for P243

SEQ ID NO: 171 is the determined cDNA sequence for P703P-DE1

SEQ ID NO: 172 is the predicted amino acid sequence for P703P-DE1

SEQ ID NO: 173 is the determined cDNA sequence for P703P-DE2

SEQ ID NO: 174 is the determined cDNA sequence for P703P-DE6

SEQ ID NO: 175 is the determined cDNA sequence for P703P-DE13

SEQ ID NO: 176 is the predicted amino acid sequence for P703P-DE13

SEQ ID NO: 177 is the determined cDNA sequence for P703P-DE14

SEQ ID NO: 178 is the predicted amino acid sequence for P703P-DE14

SEQ ID NO: 179 is the determined extended cDNA sequence for 1G-4736

SEQ ID NO: 180 is the determined extended cDNA sequence for 1G-4738

SEQ ID NO: 181 is the determined extended cDNA sequence for 1G-4741

SEQ ID NO: 182 is the determined extended cDNA sequence for 1G-4744

SEQ ID NO: 183 is the determined extended cDNA sequence for 1H-4774

SEQ ID NO: 184 is the determined extended cDNA sequence for 1H-4781

SEQ ID NO: 185 is the determined extended cDNA sequence for 1H-4785

SEQ ID NO: 186 is the determined extended cDNA sequence for 1H-4787

SEQ ID NO: 187 is the determined extended cDNA sequence for 1H-4796

SEQ ID NO: 188 is the determined extended cDNA sequence for 1I-4807

SEQ ID NO: 189 is the determined 3' cDNA sequence for 1I-4810

SEQ ID NO: 190 is the determined 3' cDNA sequence for 1I-4811

SEQ ID NO: 191 is the determined extended cDNA sequence for 1J-4876

SEQ ID NO: 192 is the determined extended cDNA sequence for 1K-4884

SEQ ID NO: 193 is the determined extended cDNA sequence for 1K-4896

SEQ ID NO: 194 is the determined extended cDNA sequence for 1G-4761

SEQ ID NO: 195 is the determined extended cDNA sequence for 1G-4762

SEQ ID NO: 196 is the determined extended cDNA sequence for 1H-4766

SEQ ID NO: 197 is the determined 3' cDNA sequence for 1H-4770

SEQ ID NO: 198 is the determined 3' cDNA sequence for 1H-4771

SEQ ID NO: 199 is the determined extended cDNA sequence for 1H-4772

SEQ ID NO: 200 is the determined extended cDNA sequence for 1D-4309

SEQ ID NO: 201 is the determined extended cDNA sequence for 1D.1-4278

SEQ ID NO: 202 is the determined extended cDNA sequence for 1D-4288

SEQ ID NO: 203 is the determined extended cDNA sequence for 1D-4283

SEQ ID NO: 204 is the determined extended cDNA sequence for 1D-4304

SEQ ID NO: 205 is the determined extended cDNA sequence for 1D-4296

SEQ ID NO: 206 is the determined extended cDNA sequence for 1D-4280

SEQ ID NO: 207 is the determined cDNA sequence for 10-d8fwd

SEQ ID NO: 208 is the determined cDNA sequence for 10-H10con

SEQ ID NO: 209 is the determined cDNA sequence for 11-C8rev

SEQ ID NO: 210 is the determined cDNA sequence for 7.g6fwd

SEQ ID NO: 211 is the determined cDNA sequence for 7.g6rev

SEQ ID NO: 212 is the determined cDNA sequence for 8-b5fwd

SEQ ID NO: 213 is the determined cDNA sequence for 8-b5rev

SEQ ID NO: 214 is the determined cDNA sequence for 8-b6fwd

SEQ ID NO: 215 is the determined cDNA sequence for 8-b6 rev

SEQ ID NO: 216 is the determined cDNA sequence for 8-d4fwd

SEQ ID NO: 217 is the determined cDNA sequence for 8-d9rev

SEQ ID NO: 218 is the determined cDNA sequence for 8-g3fwd

SEQ ID NO: 219 is the determined cDNA sequence for 8-g3rev

SEQ ID NO: 220 is the determined cDNA sequence for 8-h11rev

SEQ ID NO: 221 is the determined cDNA sequence for g-f12fwd

SEQ ID NO: 222 is the determined cDNA sequence for g-f3rev

SEQ ID NO: 223 is the determined cDNA sequence for P509S

SEQ ID NO: 224 is the determined cDNA sequence for P510S

SEQ ID NO: 225 is the determined cDNA sequence for P703DE5

SEQ ID NO: 226 is the determined cDNA sequence for 9-A11

SEQ ID NO: 227 is the determined cDNA sequence for 8-C6

SEQ ID NO: 228 is the determined cDNA sequence for 8-H7

SEQ ID NO: 229 is the determined cDNA sequence for JPTPN13

SEQ ID NO: 230 is the determined cDNA sequence for JPTPN14

SEQ ID NO: 231 is the determined cDNA sequence for JPTPN23

SEQ ID NO: 232 is the determined cDNA sequence for JPTPN24

SEQ ID NO: 233 is the determined cDNA sequence for JPTPN25

SEQ ID NO: 234 is the determined cDNA sequence for JPTPN30

SEQ ID NO: 235 is the determined cDNA sequence for JPTPN34

SEQ ID NO: 236 is the determined cDNA sequence for PTPN35

SEQ ID NO: 237 is the determined cDNA sequence for JPTPN36

SEQ ID NO: 238 is the determined cDNA sequence for JPTPN38

SEQ ID NO: 239 is the determined cDNA sequence for JPTPN39

SEQ ID NO: 240 is the determined cDNA sequence for JPTPN40

SEQ ID NO: 241 is the determined cDNA sequence for JPTPN41

SEQ ID NO: 242 is the determined cDNA sequence for JPTPN42

SEQ ID NO: 243 is the determined cDNA sequence for JPTPN45
SEQ ID NO: 244 is the determined cDNA sequence for JPTPN46
SEQ ID NO: 245 is the determined cDNA sequence for JPTPN51
SEQ ID NO: 246 is the determined cDNA sequence for JPTPN56
SEQ ID NO: 247 is the determined cDNA sequence for PTPN64
SEQ ID NO: 248 is the determined cDNA sequence for JPTPN65
SEQ ID NO: 249 is the determined cDNA sequence for JPTPN67
SEQ ID NO: 250 is the determined cDNA sequence for JPTPN76
SEQ ID NO: 251 is the determined cDNA sequence for JPTPN84
SEQ ID NO: 252 is the determined cDNA sequence for JPTPN85
SEQ ID NO: 253 is the determined cDNA sequence for JPTPN86
SEQ ID NO: 254 is the determined cDNA sequence for JPTPN87
SEQ ID NO: 255 is the determined cDNA sequence for JPTPN88
SEQ ID NO: 256 is the determined cDNA sequence for JP1F1
SEQ ID NO: 257 is the determined cDNA sequence for JP1F2
SEQ ID NO: 258 is the determined cDNA sequence for JP1C2
SEQ ID NO: 259 is the determined cDNA sequence for JP1B1
SEQ ID NO: 260 is the determined cDNA sequence for JP1B2
SEQ ID NO: 261 is the determined cDNA sequence for JP1D3
SEQ ID NO: 262 is the determined cDNA sequence for JP1A4
SEQ ID NO: 263 is the determined cDNA sequence for JP1F5
SEQ ID NO: 264 is the determined cDNA sequence for JP1E6
SEQ ID NO: 265 is the determined cDNA sequence for JP1D6
SEQ ID NO: 266 is the determined cDNA sequence for JP1B5
SEQ ID NO: 267 is the determined cDNA sequence for JP1A6
SEQ ID NO: 268 is the determined cDNA sequence for JP1E8
SEQ ID NO: 269 is the determined cDNA sequence for JP1D7
SEQ ID NO: 270 is the determined cDNA sequence for JP1D9
SEQ ID NO: 271 is the determined cDNA sequence for JP1C10
SEQ ID NO: 272 is the determined cDNA sequence for JP1A9

SEQ ID NO: 273 is the determined cDNA sequence for JP1F12
SEQ ID NO: 274 is the determined cDNA sequence for JP1E12
SEQ ID NO: 275 is the determined cDNA sequence for JP1D11
SEQ ID NO: 276 is the determined cDNA sequence for JP1C11
SEQ ID NO: 277 is the determined cDNA sequence for JP1C12
SEQ ID NO: 278 is the determined cDNA sequence for JP1B12
SEQ ID NO: 279 is the determined cDNA sequence for JP1A12
SEQ ID NO: 280 is the determined cDNA sequence for JP8G2
SEQ ID NO: 281 is the determined cDNA sequence for JP8H1
SEQ ID NO: 282 is the determined cDNA sequence for JP8H2
SEQ ID NO: 283 is the determined cDNA sequence for JP8A3
SEQ ID NO: 284 is the determined cDNA sequence for JP8A4
SEQ ID NO: 285 is the determined cDNA sequence for JP8C3
SEQ ID NO: 286 is the determined cDNA sequence for JP8G4
SEQ ID NO: 287 is the determined cDNA sequence for JP8B6
SEQ ID NO: 288 is the determined cDNA sequence for JP8D6
SEQ ID NO: 289 is the determined cDNA sequence for JP8F5
SEQ ID NO: 290 is the determined cDNA sequence for JP8A8
SEQ ID NO: 291 is the determined cDNA sequence for JP8C7
SEQ ID NO: 292 is the determined cDNA sequence for JP8D7
SEQ ID NO: 293 is the determined cDNA sequence for P8D8
SEQ ID NO: 294 is the determined cDNA sequence for JP8E7
SEQ ID NO: 295 is the determined cDNA sequence for JP8F8
SEQ ID NO: 296 is the determined cDNA sequence for JP8G8
SEQ ID NO: 297 is the determined cDNA sequence for JP8B10
SEQ ID NO: 298 is the determined cDNA sequence for JP8C10
SEQ ID NO: 299 is the determined cDNA sequence for JP8E9
SEQ ID NO: 300 is the determined cDNA sequence for JP8E10
SEQ ID NO: 301 is the determined cDNA sequence for JP8F9
SEQ ID NO: 302 is the determined cDNA sequence for JP8H9

SEQ ID NO: 303 is the determined cDNA sequence for JP8C12

SEQ ID NO: 304 is the determined cDNA sequence for JP8E11

SEQ ID NO: 305 is the determined cDNA sequence for JP8E12

SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12

SEQ ID NO: 307 is the determined cDNA sequence for P711P

SEQ ID NO: 308 is the determined cDNA sequence for P712P

SEQ ID NO: 309 is the determined cDNA sequence for CLONE23

SEQ ID NO: 310 is the determined cDNA sequence for P774P

SEQ ID NO: 311 is the determined cDNA sequence for P775P

SEQ ID NO: 312 is the determined cDNA sequence for P715P

SEQ ID NO: 313 is the determined cDNA sequence for P710P

SEQ ID NO: 314 is the determined cDNA sequence for P767P

SEQ ID NO: 315 is the determined cDNA sequence for P768P

SEQ ID NO: 316-325 are the determined cDNA sequences of previously isolated genes

SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5

SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5

SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26

SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26

SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23

SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23

SEQ ID NO: 332 is the determined full length cDNA sequence for P509S

SEQ ID NO: 333 is the determined extended cDNA sequence for P707P (also referred to as 11-C9)

SEQ ID NO: 334 is the determined cDNA sequence for P714P

SEQ ID NO: 335 is the determined cDNA sequence for P705P (also referred to as 9-F3)

SEQ ID NO: 336 is the predicted amino acid sequence for P705P

SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10

SEQ ID NO: 338 is the amino acid sequence of the peptide p5

SEQ ID NO: 339 is the predicted amino acid sequence of P509S

SEQ ID NO: 340 is the determined cDNA sequence for P778P

SEQ ID NO: 341 is the determined cDNA sequence for P786P

SEQ ID NO: 342 is the determined cDNA sequence for P789P

SEQ ID NO: 343 is the determined cDNA sequence for a clone showing homology to Homo sapiens MM46 mRNA

SEQ ID NO: 344 is the determined cDNA sequence for a clone showing homology to Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA

SEQ ID NO: 345 is the determined cDNA sequence for a clone showing homology to Homo sapiens mRNA for E-cadherin

SEQ ID NO: 346 is the determined cDNA sequence for a clone showing homology to Human nuclear-encoded mitochondrial serine hydroxymethyltransferase (SHMT)

SEQ ID NO: 347 is the determined cDNA sequence for a clone showing homology to Homo sapiens natural resistance-associated macrophage protein2 (NRAMP2)

SEQ ID NO: 348 is the determined cDNA sequence for a clone showing homology to Homo sapiens phosphoglucomutase-related protein (PGMRP)

SEQ ID NO: 349 is the determined cDNA sequence for a clone showing homology to Human mRNA for proteosome subunit p40

SEQ ID NO: 350 is the determined cDNA sequence for P777P

SEQ ID NO: 351 is the determined cDNA sequence for P779P

SEQ ID NO: 352 is the determined cDNA sequence for P790P

SEQ ID NO: 353 is the determined cDNA sequence for P784P

SEQ ID NO: 354 is the determined cDNA sequence for P776P

SEQ ID NO: 355 is the determined cDNA sequence for P780P

SEQ ID NO: 356 is the determined cDNA sequence for P544S

SEQ ID NO: 357 is the determined cDNA sequence for P745S

SEQ ID NO: 358 is the determined cDNA sequence for P782P

SEQ ID NO: 359 is the determined cDNA sequence for P783P

SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984

SEQ ID NO: 361 is the determined cDNA sequence for P787P

SEQ ID NO: 362 is the determined cDNA sequence for P788P

SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994

SEQ ID NO: 364 is the determined cDNA sequence for P781P

SEQ ID NO: 365 is the determined cDNA sequence for P785P

SEQ ID NO: 366-375 are the determined cDNA sequences for splice variants of B305D.

SEQ ID NO: 376 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 366.

SEQ ID NO: 377 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 372.

SEQ ID NO: 378 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 373.

SEQ ID NO: 379 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 374.

SEQ ID NO: 380 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 375.

SEQ ID NO: 381 is the determined cDNA sequence for B716P.

SEQ ID NO: 382 is the determined full-length cDNA sequence for P711P.

SEQ ID NO: 383 is the predicted amino acid sequence for P711P.

SEQ ID NO: 384 is the cDNA sequence for P1000C.

SEQ ID NO: 385 is the cDNA sequence for CGI-82.

SEQ ID NO:386 is the cDNA sequence for 23320.

SEQ ID NO:387 is the cDNA sequence for CGI-69.

SEQ ID NO:388 is the cDNA sequence for L-iditol-2-dehydrogenase.

SEQ ID NO:389 is the cDNA sequence for 23379.

SEQ ID NO:390 is the cDNA sequence for 23381.

SEQ ID NO:391 is the cDNA sequence for KIAA0122.

SEQ ID NO:392 is the cDNA sequence for 23399.

SEQ ID NO:393 is the cDNA sequence for a previously identified gene.

SEQ ID NO:394 is the cDNA sequence for HCLBP.

SEQ ID NO:395 is the cDNA sequence for transglutaminase.

SEQ ID NO:396 is the cDNA sequence for a previously identified gene.

SEQ ID NO:397 is the cDNA sequence for PAP.

SEQ ID NO:398 is the cDNA sequence for Ets transcription factor PDEF.

SEQ ID NO:399 is the cDNA sequence for hTGR.

SEQ ID NO:400 is the cDNA sequence for KIAA0295.

SEQ ID NO:401 is the cDNA sequence for 22545.

SEQ ID NO:402 is the cDNA sequence for 22547.

SEQ ID NO:403 is the cDNA sequence for 22548.

SEQ ID NO:404 is the cDNA sequence for 22550.

SEQ ID NO:405 is the cDNA sequence for 22551.

SEQ ID NO:406 is the cDNA sequence for 22552.

SEQ ID NO:407 is the cDNA sequence for 22553 (also known as P1020C).

SEQ ID NO:408 is the cDNA sequence for 22558.

SEQ ID NO:409 is the cDNA sequence for 22562.

SEQ ID NO:410 is the cDNA sequence for 22565.

SEQ ID NO:411 is the cDNA sequence for 22567.

SEQ ID NO:412 is the cDNA sequence for 22568.

SEQ ID NO:413 is the cDNA sequence for 22570.

SEQ ID NO:414 is the cDNA sequence for 22571.

SEQ ID NO:415 is the cDNA sequence for 22572.

SEQ ID NO:416 is the cDNA sequence for 22573.

SEQ ID NO:417 is the cDNA sequence for 22573.

SEQ ID NO:418 is the cDNA sequence for 22575.

SEQ ID NO:419 is the cDNA sequence for 22580.

SEQ ID NO:420 is the cDNA sequence for 22581.

SEQ ID NO:421 is the cDNA sequence for 22582.

SEQ ID NO:422 is the cDNA sequence for 22583.

SEQ ID NO:423 is the cDNA sequence for 22584.

SEQ ID NO:424 is the cDNA sequence for 22585.

SEQ ID NO:425 is the cDNA sequence for 22586.

SEQ ID NO:426 is the cDNA sequence for 22587.

SEQ ID NO:427 is the cDNA sequence for 22588.

SEQ ID NO:428 is the cDNA sequence for 22589.

SEQ ID NO:429 is the cDNA sequence for 22590.

SEQ ID NO:430 is the cDNA sequence for 22591.

SEQ ID NO:431 is the cDNA sequence for 22592.

SEQ ID NO:432 is the cDNA sequence for 22593.

SEQ ID NO:433 is the cDNA sequence for 22594.

SEQ ID NO:434 is the cDNA sequence for 22595.

SEQ ID NO:435 is the cDNA sequence for 22596.

SEQ ID NO:436 is the cDNA sequence for 22847.

SEQ ID NO:437 is the cDNA sequence for 22848.

SEQ ID NO:438 is the cDNA sequence for 22849.

SEQ ID NO:439 is the cDNA sequence for 22851.

SEQ ID NO:440 is the cDNA sequence for 22852.

SEQ ID NO:441 is the cDNA sequence for 22853.

SEQ ID NO:442 is the cDNA sequence for 22854.

SEQ ID NO:443 is the cDNA sequence for 22855.

SEQ ID NO:444 is the cDNA sequence for 22856.

SEQ ID NO:445 is the cDNA sequence for 22857.

SEQ ID NO:446 is the cDNA sequence for 23601.

SEQ ID NO:447 is the cDNA sequence for 23602.

SEQ ID NO:448 is the cDNA sequence for 23605.

SEQ ID NO:449 is the cDNA sequence for 23606.

SEQ ID NO:450 is the cDNA sequence for 23612.

SEQ ID NO:451 is the cDNA sequence for 23614.

SEQ ID NO:452 is the cDNA sequence for 23618.

SEQ ID NO:453 is the cDNA sequence for 23622.

SEQ ID NO:454 is the cDNA sequence for folate hydrolase.

SEQ ID NO:455 is the cDNA sequence for LIM protein.

SEQ ID NO:456 is the cDNA sequence for a known gene.

SEQ ID NO:457 is the cDNA sequence for a known gene.

SEQ ID NO:458 is the cDNA sequence for a previously identified gene.

SEQ ID NO:459 is the cDNA sequence for 23045.

SEQ ID NO:460 is the cDNA sequence for 23032.

SEQ ID NO:461 is the cDNA sequence for clone 23054.

SEQ ID NO:462-467 are cDNA sequences for known genes.

SEQ ID NO:468-471 are cDNA sequences for P710P.

SEQ ID NO:472 is a cDNA sequence for P1001C.

SEQ ID NO: 473 is the determined cDNA sequence for a first splice variant of P775P (referred to as 27505).

SEQ ID NO: 474 is the determined cDNA sequence for a second splice variant of P775P (referred to as 19947).

SEQ ID NO: 475 is the determined cDNA sequence for a third splice variant of P775P (referred to as 19941).

SEQ ID NO: 476 is the determined cDNA sequence for a fourth splice variant of P775P (referred to as 19937).

SEQ ID NO: 477 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 474.

SEQ ID NO: 478 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 474.

SEQ ID NO: 479 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 475.

SEQ ID NO: 480 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 481 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 482 is a third predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 483 is a fourth predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 484 is the first 30 amino acids of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 485 is the PCR primer AW025.

SEQ ID NO: 486 is the PCR primer AW003.

SEQ ID NO: 487 is the PCR primer AW027.

SEQ ID NO: 488 is the PCR primer AW026.

SEQ ID NO: 489-501 are peptides employed in epitope mapping studies.

SEQ ID NO: 502 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody 20D4.

SEQ ID NO: 503 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody JA1.

SEQ ID NO: 504 & 505 are peptides employed in epitope mapping studies.

SEQ ID NO: 506 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 8H2.

SEQ ID NO: 507 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 7H8.

SEQ ID NO: 508 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 2D4.

SEQ ID NO: 509-522 are peptides employed in epitope mapping studies.

SEQ ID NO: 523 is a mature form of P703P used to raise antibodies against P703P.

SEQ ID NO: 524 is the putative full-length cDNA sequence of P703P.

SEQ ID NO: 525 is the predicted amino acid sequence encoded by SEQ ID NO: 524.

SEQ ID NO: 526 is the full-length cDNA sequence for P790P.

SEQ ID NO: 527 is the predicted amino acid sequence for P790P.

SEQ ID NO: 528 & 529 are PCR primers.

SEQ ID NO: 530 is the cDNA sequence of a splice variant of SEQ ID NO: 366.

SEQ ID NO: 531 is the cDNA sequence of the open reading frame of SEQ ID NO: 530.

SEQ ID NO: 532 is the predicted amino acid encoded by the sequence of SEQ ID NO: 531.

SEQ ID NO: 533 is the DNA sequence of a putative ORF of P775P.

SEQ ID NO: 534 is the predicted amino acid sequence encoded by SEQ ID NO: 533.

SEQ ID NO: 535 is a first full-length cDNA sequence for P510S.

SEQ ID NO: 536 is a second full-length cDNA sequence for P510S.

SEQ ID NO: 537 is the predicted amino acid sequence encoded by SEQ ID NO: 535.

SEQ ID NO: 538 is the predicted amino acid sequence encoded by SEQ ID NO: 536.

SEQ ID NO: 539 is the peptide P501S-370.

SEQ ID NO: 540 is the peptide P501S-376.

SEQ ID NO: 541-551 are epitopes of P501S.

SEQ ID NO: 552 is an extended cDNA sequence for P712P.

SEQ ID NO: 553-568 are the amino acid sequences encoded by predicted open reading frames within SEQ ID NO: 552.

SEQ ID NO: 569 is an extended cDNA sequence for P776P.

SEQ ID NO: 570 is the determined cDNA sequence for a splice variant of P776P referred to as contig 6.

SEQ ID NO: 571 is the determined cDNA sequence for a splice variant of P776P referred to as contig 7.

SEQ ID NO: 572 is the determined cDNA sequence for a splice variant of P776P referred to as contig 14.

SEQ ID NO: 573 is the amino acid sequence encoded by a first predicted ORF of SEQ ID NO: 570.

SEQ ID NO: 574 is the amino acid sequence encoded by a second predicted ORF of SEQ ID NO: 570.

SEQ ID NO: 575 is the amino acid sequence encoded by a predicted ORF of SEQ ID NO: 571.

SEQ ID NO: 576-586 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 569.

SEQ ID NO: 587 is a DNA consensus sequence of the sequences of P767P and P777P.

SEQ ID NO: 588-590 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 587.

SEQ ID NO: 591 is an extended cDNA sequence for P1020C.

SEQ ID NO: 592 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: P1020C.

SEQ ID NO: 593 is a splice variant of P775P referred to as 50748.

SEQ ID NO: 594 is a splice variant of P775P referred to as 50717.

SEQ ID NO: 595 is a splice variant of P775P referred to as 45985.

SEQ ID NO: 596 is a splice variant of P775P referred to as 38769.

SEQ ID NO: 597 is a splice variant of P775P referred to as 37922.

SEQ ID NO: 598 is a splice variant of P510S referred to as 49274.

SEQ ID NO: 599 is a splice variant of P510S referred to as 39487.

SEQ ID NO: 600 is a splice variant of P504S referred to as 5167.16.

SEQ ID NO: 601 is a splice variant of P504S referred to as 5167.1.

SEQ ID NO: 602 is a splice variant of P504S referred to as 5163.46.

SEQ ID NO: 603 is a splice variant of P504S referred to as 5163.42.

SEQ ID NO: 604 is a splice variant of P504S referred to as 5163.34.

SEQ ID NO: 605 is a splice variant of P504S referred to as 5163.17.

SEQ ID NO: 606 is a splice variant of P501S referred to as 10640.

SEQ ID NO: 607-615 are the sequences of PCR primers.

SEQ ID NO: 616 is the determined cDNA sequence of a fusion of P703P and PSA.

SEQ ID NO: 617 is the amino acid sequence of the fusion of P703P and PSA.

SEQ ID NO: 618 is the cDNA sequence of the gene DD3.

SEQ ID NO: 619 is an extended cDNA sequence for P714P.

SEQ ID NO: 620-622 are the cDNA sequences for splice variants of P704P.

SEQ ID NO: 623 is the cDNA sequence of a splice variant of P553S referred to as P553S-14.

SEQ ID NO: 624 is the cDNA sequence of a splice variant of P553S referred to as P553S-12.

SEQ ID NO: 625 is the cDNA sequence of a splice variant of P553S referred to as P553S-10.

SEQ ID NO: 626 is the cDNA sequence of a splice variant of P553S referred to as P553S-6.

SEQ ID NO: 627 is the amino acid sequence encoded by SEQ ID NO: 626.

SEQ ID NO: 628 is a first amino acid sequence encoded by SEQ ID NO: 623.

SEQ ID NO: 629 is a second amino acid sequence encoded by SEQ ID NO: 623.

SEQ ID NO: 630 is a first full-length cDNA sequence for prostate-specific transglutaminase gene (also referred to herein as P558S).

SEQ ID NO: 631 is a second full-length cDNA sequence for prostate-specific transglutaminase gene.

SEQ ID NO: 632 is the amino acid sequence encoded by the sequence of SEQ ID NO: 630.

SEQ ID NO: 633 is the amino acid sequence encoded by the sequence of SEQ ID NO: 631.

SEQ ID NO: 634 is the full-length cDNA sequence for P788P.

SEQ ID NO: 635 is the amino acid sequence encoded by SEQ ID NO: 634.

SEQ ID NO: 636 is the determined cDNA sequence for a polymorphic variant of P788P.

SEQ ID NO: 637 is the amino acid sequence encoded by SEQ ID NO: 636.

SEQ ID NO: 638 is the amino acid sequence of peptide 4 from P703P.

SEQ ID NO: 639 is the cDNA sequence that encodes peptide 4 from P703P.

SEQ ID NO: 640-655 are cDNA sequences encoding epitopes of P703P.

SEQ ID NO: 656-671 are the amino acid sequences of epitopes of P703P.

SEQ ID NO: 672 and 673 are PCR primers.

SEQ ID NO: 674 is the cDNA sequence encoding an N-terminal portion of P788P expressed in *E. coli*.

SEQ ID NO: 675 is the amino acid sequence of the N-terminal portion of P788P expressed in *E. coli*.

SEQ ID NO: 676 is the amino acid sequence of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 677 and 678 are PCR primers.

SEQ ID NO: 679 is the cDNA sequence for the Ra12-P510S-C construct.

SEQ ID NO: 680 is the cDNA sequence for the P510S-C construct.

SEQ ID NO: 681 is the cDNA sequence for the P510S-E3 construct.

SEQ ID NO: 682 is the amino acid sequence for the Ra12-P510S-C construct.

SEQ ID NO: 683 is the amino acid sequence for the P510S-C construct.

SEQ ID NO: 684 is the amino acid sequence for the P510S-E3 construct.

SEQ ID NO: 685-690 are PCR primers.

SEQ ID NO: 691 is the cDNA sequence of the construct Ra12-P775P-ORF3.

SEQ ID NO: 692 is the amino acid sequence of the construct Ra12-P775P-ORF3.

SEQ ID NO: 693 and 694 are PCR primers.

SEQ ID NO: 695 is the determined amino acid sequence for a P703P His tag fusion protein.

SEQ ID NO: 696 is the determined cDNA sequence for a P703P His tag fusion protein.

SEQ ID NO: 697 and 698 are PCR primers.

SEQ ID NO: 699 is the determined amino acid sequence for a P705P His tag fusion protein.

SEQ ID NO: 700 is the determined cDNA sequence for a P705P His tag fusion protein.

SEQ ID NO: 701 and 702 are PCR primers.

SEQ ID NO: 703 is the determined amino acid sequence for a P711P His tag fusion protein.

SEQ ID NO: 704 is the determined cDNA sequence for a P711P His tag fusion protein.

SEQ ID NO: 705 is the amino acid sequence of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 706 and 707 are PCR primers.

SEQ ID NO: 708 is the determined cDNA sequence for the construct Ra12-P501S-E2.

SEQ ID NO: 709 is the determined amino acid sequence for the construct Ra12-P501S-E2.

SEQ ID NO: 710 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 711 is the DNA sequence encoding SEQ ID NO: 710.

SEQ ID NO: 712 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 713 is the DNA sequence encoding SEQ ID NO: 712.

SEQ ID NO: 714 is a peptide employed in epitope mapping studies.

SEQ ID NO: 715 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 716 is the DNA sequence encoding SEQ ID NO: 715.

SEQ ID NO: 717-719 are the amino acid sequences for CD4 epitopes of P501S.

SEQ ID NO: 720-722 are the DNA sequences encoding the sequences of SEQ ID NO: 717-719.

SEQ ID NO: 723-734 are the amino acid sequences for putative CTL epitopes of P703P.

SEQ ID NO: 735 is the full-length cDNA sequence for P789P.

SEQ ID NO: 736 is the amino acid sequence encoded by SEQ ID NO: 735.

SEQ ID NO: 737 is the determined full-length cDNA sequence for the splice variant of P776P referred to as contig 6.

SEQ ID NO: 738-739 are determined full-length cDNA sequences for the splice variant of P776P referred to as contig 7.

SEQ ID NO: 740-744 are amino acid sequences encoded by SEQ ID NO: 737.

SEQ ID NO: 745-750 are amino acid sequences encoded by the splice variant of P776P referred to as contig 7.

SEQ ID NO: 751 is the full-length cDNA sequence for human transmembrane protease serine 2.

SEQ ID NO: 752 is the amino acid sequence encoded by SEQ ID NO: 751.

SEQ ID NO: 753 is the cDNA sequence encoding the first 209 amino acids of human transmembrane protease serine 2.

SEQ ID NO: 754 is the first 209 amino acids of human transmembrane protease serine 2.

SEQ ID NO: 755 is the amino acid sequence of peptide 296-322 of P501S.

SEQ ID NO: 756-759 are PCR primers.

SEQ ID NO: 760 is the determined cDNA sequence of the Vb chain of a T cell receptor for the P501S-specific T cell clone 4E5.

SEQ ID NO: 761 is the determined cDNA sequence of the Va chain of a T cell receptor for the P501S-specific T cell clone 4E5.

SEQ ID NO: 762 is the amino acid sequence encoded by SEQ ID NO 760.

SEQ ID NO: 763 is the amino acid sequence encoded by SEQ ID NO 761.

SEQ ID NO: 764 is the full-length open reading frame for P768P including stop codon.

SEQ ID NO: 765 is the full-length open reading frame for P768P without stop codon.

SEQ ID NO: 766 is the amino acid sequence encoded by SEQ ID NO: 765.

SEQ ID NO: 767-772 are the amino acid sequences for predicted domains of P768P.

SEQ ID NO: 773 is the full-length cDNA sequence of P835P.

SEQ ID NO: 774 is the cDNA sequence of the previously identified clone FLJ13581.

SEQ ID NO: 775 is the cDNA sequence of the open reading frame for P835P with stop codon.

SEQ ID NO: 776 is the cDNA sequence of the open reading frame for P835P without stop codon.

SEQ ID NO: 777 is the full-length amino acid sequence for P835P.

SEQ ID NO: 778-785 are the amino acid sequences of extracellular and intracellular domains of P835P.

SEQ ID NO: 786 is the full-length cDNA sequence for P1000C.

SEQ ID NO: 787 is the cDNA sequence of the open reading frame for P1000C, including stop codon.

SEQ ID NO: 788 is the cDNA sequence of the open reading frame for P1000C, without stop codon.

SEQ ID NO: 789 is the full-length amino acid sequence for P1000C.

SEQ ID NO: 790 is amino acids 1-100 of SEQ ID NO: 789.

SEQ ID NO: 791 is amino acids 100-492 of SEQ ID NO: 789.

SEQ ID NO: 792 is the amino acid sequence of an α prepro-P501S recombinant protein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to compositions and their use in the therapy and diagnosis of cancer, particularly prostate cancer. As described further below, illustrative compositions of the present invention include, but are not restricted to, polypeptides, particularly immunogenic polypeptides, polynucleotides encoding such polypeptides, antibodies and other binding agents, antigen presenting cells (APCs) and immune system cells (*e.g.,* T cells).

The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, *e.g.*, Sambrook, et al. Molecular Cloning: A Laboratory Manual (2nd Edition, 1989); Maniatis et al. Molecular Cloning: A Laboratory Manual (1982); DNA Cloning: A Practical Approach, vol. I & II (D. Glover, ed.); Oligonucleotide Synthesis (N. Gait, ed., 1984); Nucleic Acid

Hybridization (B. Hames & S. Higgins, eds., 1985); Transcription and Translation (B. Hames & S. Higgins, eds., 1984); Animal Cell Culture (R. Freshney, ed., 1986); Perbal, A Practical Guide to Molecular Cloning (1984).

All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise.

Polypeptide Compositions

As used herein, the term "polypeptide" " is used in its conventional meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a specific length of the product; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or exclude post-expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof. Particular polypeptides of interest in the context of this invention are amino acid subsequences comprising epitopes, *i.e.*, antigenic determinants substantially responsible for the immunogenic properties of a polypeptide and being capable of evoking an immune response.

Particularly illustrative polypeptides of the present invention comprise those encoded by a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, or a sequence that hybridizes under moderately stringent conditions, or, alternatively, under highly stringent conditions, to a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175,

177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788. In specific embodiments, the polypeptides of the invention comprise amino acid sequences as set forth in any one of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791.

The polypeptides of the present invention are sometimes herein referred to as prostate-specific proteins or prostate-specific polypeptides, as an indication that their identification has been based at least in part upon their increased levels of expression in prostate tissue samples. Thus, a "prostate-specific polypeptide" or "prostate-specific protein," refers generally to a polypeptide sequence of the present invention, or a polynucleotide sequence encoding such a polypeptide, that is expressed in a substantial proportion of prostate tissue samples, for example preferably greater than about 20%, more preferably greater than about 30%, and most preferably greater than about 50% or more of prostate tissue samples tested, at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in other normal tissues, as determined using a representative assay provided herein. A prostate-specific polypeptide sequence of the invention, based upon its increased level of expression in tumor cells, has particular utility both as a diagnostic marker as well as a therapeutic target, as further described below.

In certain preferred embodiments, the polypeptides of the invention are immunogenic, *i.e.*, they react detectably within an immunoassay (such as an ELISA or T-cell stimulation assay) with antisera and/or T-cells from a patient with prostate cancer. Screening for immunogenic activity can be performed using techniques well known to the skilled artisan. For example, such screens can be performed using methods such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. In one illustrative example, a

polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A.

As would be recognized by the skilled artisan, immunogenic portions of the polypeptides disclosed herein are also encompassed by the present invention. An "immunogenic portion," as used herein, is a fragment of an immunogenic polypeptide of the invention that itself is immunologically reactive (*i.e.*, specifically binds) with the B-cells and/or T-cell surface antigen receptors that recognize the polypeptide. Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well-known techniques.

In one preferred embodiment, an immunogenic portion of a polypeptide of the present invention is a portion that reacts with antisera and/or T-cells at a level that is not substantially less than the reactivity of the full-length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Preferably, the level of immunogenic activity of the immunogenic portion is at least about 50%, preferably at least about 70% and most preferably greater than about 90% of the immunogenicity for the full-length polypeptide. In some instances, preferred immunogenic portions will be identified that have a level of immunogenic activity greater than that of the corresponding full-length polypeptide, *e.g.*, having greater than about 100% or 150% or more immunogenic activity.

In certain other embodiments, illustrative immunogenic portions may include peptides in which an N-terminal leader sequence and/or transmembrane domain has been deleted. Other illustrative immunogenic portions will contain a small N-

and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

In another embodiment, a polypeptide composition of the invention may also comprise one or more polypeptides that are immunologically reactive with T cells and/or antibodies generated against a polypeptide of the invention, particularly a polypeptide having an amino acid sequence disclosed herein, or to an immunogenic fragment or variant thereof.

In another embodiment of the invention, polypeptides are provided that comprise one or more polypeptides that are capable of eliciting T cells and/or antibodies that are immunologically reactive with one or more polypeptides described herein, or one or more polypeptides encoded by contiguous nucleic acid sequences contained in the polynucleotide sequences disclosed herein, or immunogenic fragments or variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

The present invention, in another aspect, provides polypeptide fragments comprising at least about 5, 10, 15, 20, 25, 50, or 100 contiguous amino acids, or more, including all intermediate lengths, of a polypeptide composition set forth herein, such as those set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791, or those encoded by a polynucleotide sequence set forth in a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

In another aspect, the present invention provides variants of the polypeptide compositions described herein. Polypeptide variants generally encompassed by the present invention will typically exhibit at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity

(determined as described below), along its length, to a polypeptide sequence set forth herein.

In one preferred embodiment, the polypeptide fragments and variants provided by the present invention are immunologically reactive with an antibody and/or T-cell that reacts with a full-length polypeptide specifically set forth herein.

In another preferred embodiment, the polypeptide fragments and variants provided by the present invention exhibit a level of immunogenic activity of at least about 50%, preferably at least about 70%, and most preferably at least about 90% or more of that exhibited by a full-length polypeptide sequence specifically set forth herein.

A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the invention and evaluating their immunogenic activity as described herein using any of a number of techniques well known in the art.

For example, certain illustrative variants of the polypeptides of the invention include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other illustrative variants include variants in which a small portion (*e.g.,* 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

In many instances, a variant will contain conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. As described above, modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics, *e.g.*, with immunogenic characteristics. When it is desired to alter the amino acid sequence of a polypeptide to create an equivalent, or

even an improved, immunogenic variant or portion of a polypeptide of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids			Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its

hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (–0.4); threonine (–0.7); serine (–0.8); tryptophan (–0.9); tyrosine (–1.3); proline (–1.6); histidine (–3.2); glutamate (–3.5); glutamine (–3.5); aspartate (–3.5); asparagine (–3.5); lysine (–3.9); and arginine (–4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 ± 1); glutamate (+3.0 ± 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (–0.4); proline (–0.5 ± 1); alanine (–0.5); histidine (–0.5); cysteine (–1.0); methionine (–1.3); valine (–1.5); leucine (–1.8); isoleucine (–1.8); tyrosine (–2.3); phenylalanine (–2.5); tryptophan (–3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those

of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

When comparing polypeptide sequences, two sequences are said to be "identical" if the sequence of amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics

Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment.

In one preferred approach, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.,* gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.,* the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Within other illustrative embodiments, a polypeptide may be a fusion polypeptide that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known

tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the polypeptide or to enable the polypeptide to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the polypeptide.

Fusion polypeptides may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion polypeptide is expressed as a recombinant polypeptide, allowing the production of increased levels, relative to a non-fused polypeptide, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion polypeptide that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion polypeptide using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al.,

Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

The fusion polypeptide can comprise a polypeptide as described herein together with an unrelated immunogenic protein, such as an immunogenic protein capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see*, for example, Stoute et al. *New Engl. J. Med.*, *336*:86-91, 1997).

In one preferred embodiment, the immunological fusion partner is derived from a Mycobacterium sp., such as a *Mycobacterium tuberculosis*-derived Ra12 fragment. Ra12 compositions and methods for their use in enhancing the expression and/or immunogenicity of heterologous polynucleotide/polypeptide sequences is described in U.S. Patent Application 60/158,585, the disclosure of which is incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application 60/158,585; see also, Skeiky *et al.*, *Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). C-terminal fragments of the MTB32A coding sequence express at high levels and remain as a soluble polypeptides throughout the purification process. Moreover, Ra12 may enhance the immunogenicity of heterologous

immunogenic polypeptides with which it is fused. One preferred Ra12 fusion polypeptide comprises a 14 KD C-terminal fragment corresponding to amino acid residues 192 to 323 of MTB32A. Other preferred Ra12 polynucleotides generally comprise at least about 15 consecutive nucleotides, at least about 30 nucleotides, at least about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300 nucleotides that encode a portion of a Ra12 polypeptide. Ra12 polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a Ra12 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ra12 polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide comprising a native Ra12 polypeptide. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ra12 polypeptide or a portion thereof.

Within other preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine

amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion polypeptide. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

Yet another illustrative embodiment involves fusion polypeptides, and the polynucleotides encoding them, wherein the fusion partner comprises a targeting signal capable of directing a polypeptide to the endosomal/lysosomal compartment, as described in U.S. Patent No. 5,633,234. An immunogenic polypeptide of the invention, when fused with this targeting signal, will associate more efficiently with MHC class II molecules and thereby provide enhanced in vivo stimulation of $CD4^+$ T-cells specific for the polypeptide.

Polypeptides of the invention are prepared using any of a variety of well known synthetic and/or recombinant techniques, the latter of which are further described below. Polypeptides, portions and other variants generally less than about 150 amino acids can be generated by synthetic means, using techniques well known to those of ordinary skill in the art. In one illustrative example, such polypeptides are synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc. 85*:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptide compositions (including fusion polypeptides) of the invention are isolated. An "isolated" polypeptide is one that is removed from its

original environment. For example, a naturally-occurring protein or polypeptide is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are also purified, *e.g.*, are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure.

Polynucleotide Compositions

The present invention, in other aspects, provides polynucleotide compositions. The terms "DNA" and "polynucleotide" are used essentially interchangeably herein to refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA molecule does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA molecule as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be understood by those skilled in the art, the polynucleotide compositions of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a polypeptide/protein of the invention or a portion thereof) or may comprise a sequence that encodes a variant or derivative, preferably an immunogenic variant or derivative, of such a sequence.

Therefore, according to another aspect of the present invention, polynucleotide compositions are provided that comprise some or all of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, complements of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, and degenerate variants of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788. In certain preferred embodiments, the polynucleotide sequences set forth herein encode immunogenic polypeptides, as described above.

In other related embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein in SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, for example those comprising at least 70% sequence identity, preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide sequence of this invention using the methods described herein, (*e.g.*,

BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

Typically, polynucleotide variants will contain one or more substitutions, additions, deletions and/or insertions, preferably such that the immunogenicity of the polypeptide encoded by the variant polynucleotide is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth herein). The term “variants” should also be understood to encompasses homologous genes of xenogenic origin.

In additional embodiments, the present invention provides polynucleotide fragments comprising various lengths of contiguous stretches of sequence identical to, or complementary to, one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

In another embodiment of the invention, polynucleotide compositions are provided that are capable of hybridizing under moderate to high stringency conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-60°C, 5 X SSC, overnight; followed by washing twice at 65°C for

20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. One skilled in the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, *e.g.*, to 60-65°C or 65-70°C.

In certain preferred embodiments, the polynucleotides described above, *e.g.*, polynucleotide variants, fragments and hybridizing sequences, encode polypeptides that are immunologically cross-reactive with a polypeptide sequence specifically set forth herein. In other preferred embodiments, such polynucleotides encode polypeptides that have a level of immunogenic activity of at least about 50%, preferably at least about 70%, and more preferably at least about 90% of that for a polypeptide sequence specifically set forth herein.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative polynucleotide segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

When comparing polynucleotide sequences, two sequences are said to be "identical" if the sequence of nucleotides in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison

window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, preferably 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST

2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.,* gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.,* the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides

that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, is employed for the preparation of immunogenic variants and/or derivatives of the polypeptides described herein. By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provides a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the immunogenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25

nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

In another approach for the production of polypeptide variants of the present invention, recursive sequence recombination, as described in U.S. Patent No. 5,837,458, may be employed. In this approach, iterative cycles of recombination and screening or selection are performed to "evolve" individual polynucleotide variants of the invention having, for example, enhanced immunogenic activity.

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 contiguous nucleotides that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of

complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequences set forth herein, or to any continuous portion of the sequences, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various

factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to

destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

According to another embodiment of the present invention, polynucleotide compositions comprising antisense oligonucleotides are provided. Antisense oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of antisense oligonucleotides for inhibiting protein synthesis is well established. For example, the synthesis of polygalactauronase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal $GABA_A$ receptor and human EGF (Jaskulski *et al.*, Science. 1988 Jun 10;240(4858):1544-6; Vasanthakumar and Ahmed, Cancer Commun. 1989;1(4):225-32; Peris *et al.*, Brain Res Mol Brain Res. 1998 Jun 15;57(2):310-20; U. S. Patent 5,801,154; U.S. Patent 5,789,573; U. S. Patent 5,718,709 and U.S. Patent 5,610,288). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683).

Therefore, in certain embodiments, the present invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary,

and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure, T_m, binding energy, and relative stability. Antisense compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell. Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which are substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations can be performed, for example, using v.4 of the OLIGO primer analysis software and/or the BLASTN 2.0.5 algorithm software (Altschul *et al.,* Nucleic Acids Res. 1997 Sep 1;25(17):3389-402).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, Nucleic Acids Res. 1997 Jul 15;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane.

According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of ribozyme molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, Proc Natl Acad Sci U S A. 1987 Dec;84(24):8788-92; Forster and Symons, Cell. 1987 Apr 24;49(2):211-20). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a

high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, Cell. 1981 Dec;27(3 Pt 2):487-96; Michel and Westhof, J Mol Biol. 1990 Dec 5;216(3):585-610; Reinhold-Hurek and Shub, Nature. 1992 May 14;357(6374):173-6). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7305-9). Thus, the

specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* Nucleic Acids Res. 1992 Sep 11;20(17):4559-65. Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz, Biochemistry 1989 Jun 13;28(12):4929-33; Hampel *et al.,* Nucleic Acids Res. 1990 Jan 25;18(2):299-304 and U. S. Patent 5,631,359. An example of the hepatitis δ virus motif is described by Perrotta and Been, Biochemistry. 1992 Dec 1;31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada *et al.*, Cell. 1983 Dec;35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, Cell. 1990 May 18;61(4):685-96; Saville and Collins, Proc Natl Acad Sci U S A. 1991 Oct 1;88(19):8826-30; Collins and Olive, Biochemistry. 1993 Mar 23;32(11):2795-9); and an example of the Group I intron is described in (U. S. Patent 4,987,071). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO

92/07065; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells Ribozymes

expressed from such promoters have been shown to function in mammalian cells. Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

In another embodiment of the invention, peptide nucleic acids (PNAs) compositions are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, Antisense Nucleic Acid Drug Dev. 1997 7(4) 431-37). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (*Trends Biotechnol* 1997 Jun;15(6):224-9). As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, *Science* 1991 Dec 6;254(5037):1497-500; Hanvey *et al.*, Science. 1992 Nov 27;258(5087):1481-5; Hyrup and Nielsen, Bioorg Med Chem. 1996 Jan;4(1):5-23). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc or Fmoc protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used.

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*,

Bioorg Med Chem. 1995 Apr;3(4):437-45). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography, providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (for example, Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45; Petersen *et al.*, J Pept Sci. 1995 May-Jun;1(3):175-83; Orum *et al.*, Biotechniques. 1995 Sep;19(3):472-80; Footer *et al.*, Biochemistry. 1996 Aug 20;35(33):10673-9; Griffith *et al.*, Nucleic Acids Res. 1995 Aug 11;23(15):3003-8; Pardridge *et al.*, Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5592-6; Boffa *et al.*, Proc Natl Acad Sci U S A. 1995 Mar 14;92(6):1901-5; Gambacorti-Passerini *et al.*, Blood. 1996 Aug 15;88(4):1411-7; Armitage *et al.*, Proc Natl Acad Sci U S A. 1997 Nov 11;94(23):12320-5; Seeger *et al.*, Biotechniques. 1997 Sep;23(3):512-7). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (Anal Chem. 1993 Dec 15;65(24):3545-9) and Jensen *et al.* (Biochemistry. 1997 Apr 22;36(16):5072-7). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, antisense inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of transcriptionally active genes, blocking of transcription factor binding, genome cleavage, biosensors, *in situ* hybridization, and the like.

Polynucleotide Identification, Characterization and Expression

Polynucleotide compositions of the present invention may be identified, prepared and/or manipulated using any of a variety of well established techniques (see generally, Sambrook et al., *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989, and other like references). For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.,* expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using the microarray technology of Affymetrix, Inc. (Santa Clara, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as tumor cells.

Many template dependent processes are available to amplify a target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by

reference in its entirety. Briefly, in PCR™, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Any of a number of other template dependent processes, many of which are variations of the PCR ™ amplification technique, are readily known and available in the art. Illustratively, some such methods include the ligase chain reaction (referred to as LCR), described, for example, in Eur. Pat. Appl. Publ. No. 320,308 and U.S. Patent No. 4,883,750; Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880; Strand Displacement Amplification (SDA) and Repair Chain Reaction (RCR). Still other amplification methods are described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025. Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (PCT Intl. Pat. Appl. Publ. No. WO 88/10315), including nucleic acid sequence based amplification (NASBA) and 3SR. Eur. Pat. Appl. Publ. No. 329,822 describes a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA). PCT Intl. Pat. Appl. Publ. No. WO 89/06700 describes a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. Other amplification methods such as "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) are also well-known to those of skill in the art.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (*e.g.*, a tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.*, by nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, amplification techniques, such as those described above, can be useful for obtaining a full length coding sequence from a partial cDNA sequence. One such amplification technique is inverse PCR (*see* Triglia et al., *Nucl. Acids Res. 16*:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of

amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids. Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) *Science 269*:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, T. (1983) Proteins, Structures and Molecular Principles, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be

confirmed by amino acid analysis or sequencing (*e.g.*, the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. et al. (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York. N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (*e.g.*, baculovirus); plant cell systems transformed with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used.

For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, any of a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem. 264*:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, Saccharomyces cerevisiae, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel et al. (supra) and Grant et al. (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For

example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J. 6*:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. et al. (1984) *EMBO J. 3*:1671-1680; Broglie, R. et al. (1984) *Science 224*:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ. 17*:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in Spodoptera frugiperda cells or in Trichoplusia larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, S. frugiperda cells or Trichoplusia larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci. 91* :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci. 81*:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) *Results Probl. Cell Differ. 20*:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation. glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, COS, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which

successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) *Cell 11*:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) *Cell 22*:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol. 150*:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci. 85*:8047-51). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) *Methods Mol. Biol. 55*:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells that contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of

skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include, for example, membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. et al. (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul. Minn.) and Maddox, D. E. et al. (1983; *J. Exp. Med. 158*:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood

by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen. San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, *Prot. Exp. Purif.* *3*:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; *DNA Cell Biol.* *12*:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* *85*:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

Antibody Compositions, Fragments Thereof and Other Binding Agents

According to another aspect, the present invention further provides binding agents, such as antibodies and antigen-binding fragments thereof, that exhibit immunological binding to a tumor polypeptide disclosed herein, or to a portion, variant or derivative thereof. An antibody, or antigen-binding fragment thereof, is said to "specifically bind," "immunogically bind," and/or is "immunologically reactive" to a polypeptide of the invention if it reacts at a detectable level (within, for example, an ELISA assay) with the polypeptide, and does not react detectably with unrelated polypeptides under similar conditions.

Immunological binding, as used in this context, generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of K_{off}/K_{on} enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant K_d. See, generally, Davies et al. (1990) Annual Rev. Biochem. 59:439-473.

An "antigen-binding site," or "binding portion" of an antibody refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable regions" which are interposed between more conserved flanking stretches known as

"framework regions," or "FRs". Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs."

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. For example, antibodies or other binding agents that bind to a tumor protein will preferably generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, more preferably at least about 30% of patients. Alternatively, or in addition, the antibody will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. Preferably, a statistically significant number of samples with and without the disease will be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation

of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.,* mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol. 6*:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

A number of therapeutically useful molecules are known in the art which comprise antigen-binding sites that are capable of exhibiting immunological binding properties of an antibody molecule. The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the "F(ab)" fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the "$F(ab')_2$ " fragment which comprises both antigen-binding sites. An "Fv" fragment can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent V_H::V_L heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar et al. (1972) Proc. Nat. Acad. Sci. USA 69:2659-2662; Hochman et al. (1976) Biochem 15:2706-2710; and Ehrlich et al. (1980) Biochem 19:4091-4096.

A single chain Fv ("sFv") polypeptide is a covalently linked V_H::V_L heterodimer which is expressed from a gene fusion including V_H- and V_L-encoding genes linked by a peptide-encoding linker. Huston et al. (1988) Proc. Nat. Acad. Sci. USA 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated--but chemically separated--light and heavy polypeptide chains from an antibody V region into an sFv molecule which will fold into a three dimensional structure substantially similar to the structure of an

antigen-binding site. See, *e.g.*, U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

Each of the above-described molecules includes a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain FR set which provide support to the CDRS and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (*e.g.*, a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRS. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures--regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

A number of "humanized" antibody molecules comprising an antigen-binding site derived from a non-human immunoglobulin have been described, including chimeric antibodies having rodent V regions and their associated CDRs fused to human constant domains (Winter et al. (1991) Nature 349:293-299; Lobuglio et al. (1989) Proc. Nat. Acad. Sci. USA 86:4220-4224; Shaw et al. (1987) J Immunol. 138:4534-4538; and Brown et al. (1987) Cancer Res. 47:3577-3583), rodent CDRs grafted into a human supporting FR prior to fusion with an appropriate human antibody constant domain (Riechmann et al. (1988) Nature 332:323-327; Verhoeyen et al. (1988) Science 239:1534-1536; and Jones et al. (1986) Nature 321:522-525), and rodent CDRs supported by recombinantly veneered rodent FRs (European Patent Publication No. 519,596, published Dec. 23, 1992). These "humanized" molecules are designed to minimize unwanted immunological response toward rodent antihuman antibody molecules which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients.

As used herein, the terms "veneered FRs" and "recombinantly veneered FRs" refer to the selective replacement of FR residues from, *e.g.*, a rodent heavy or light chain V region, with human FR residues in order to provide a xenogeneic molecule comprising an antigen-binding site which retains substantially all of the native FR polypeptide folding structure. Veneering techniques are based on the understanding that the ligand binding characteristics of an antigen-binding site are determined primarily by the structure and relative disposition of the heavy and light chain CDR sets within the antigen-binding surface. Davies et al. (1990) Ann. Rev. Biochem. 59:439-473. Thus, antigen binding specificity can be preserved in a humanized antibody only wherein the CDR structures, their interaction with each other, and their interaction with the rest of the V region domains are carefully maintained. By using veneering techniques, exterior (*e.g.*, solvent-accessible) FR residues which are readily encountered by the immune system are selectively replaced with human residues to provide a hybrid molecule that comprises either a weakly immunogenic, or substantially non-immunogenic veneered surface.

The process of veneering makes use of the available sequence data for human antibody variable domains compiled by Kabat et al., in Sequences of Proteins of Immunological Interest, 4th ed., (U.S. Dept. of Health and Human Services, U.S. Government Printing Office, 1987), updates to the Kabat database, and other accessible U.S. and foreign databases (both nucleic acid and protein). Solvent accessibilities of V region amino acids can be deduced from the known three-dimensional structure for human and murine antibody fragments. There are two general steps in veneering a murine antigen-binding site. Initially, the FRs of the variable domains of an antibody molecule of interest are compared with corresponding FR sequences of human variable domains obtained from the above-identified sources. The most homologous human V regions are then compared residue by residue to corresponding murine amino acids. The residues in the murine FR which differ from the human counterpart are replaced by the residues present in the human moiety using recombinant techniques well known in the art. Residue switching is only carried out with moieties which are at least partially exposed (solvent accessible), and care is exercised in the replacement of amino acid residues which may have a significant effect on the tertiary structure of V region domains, such as proline, glycine and charged amino acids.

In this manner, the resultant "veneered" murine antigen-binding sites are thus designed to retain the murine CDR residues, the residues substantially adjacent to the CDRs, the residues identified as buried or mostly buried (solvent inaccessible), the residues believed to participate in non-covalent (*e.g.*, electrostatic and hydrophobic) contacts between heavy and light chain domains, and the residues from conserved structural regions of the FRs which are believed to influence the "canonical" tertiary structures of the CDR loops. These design criteria are then used to prepare recombinant nucleotide sequences which combine the CDRs of both the heavy and light chain of a murine antigen-binding site into human-appearing FRs that can be used to transfect mammalian cells for the expression of recombinant human antibodies which exhibit the antigen specificity of the murine antibody molecule.

In another embodiment of the invention, monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in

this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the

intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

T Cell Compositions

The present invention, in another aspect, provides T cells specific for a tumor polypeptide disclosed herein, or for a variant or derivative thereof. Such cells

may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a polypeptide, polynucleotide encoding a polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide of interest. Preferably, a tumor polypeptide or polynucleotide of the invention is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res. 54*:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days will typically result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan et

al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a tumor polypeptide, polynucleotide or polypeptide-expressing APC may be $CD4^+$ and/or $CD8^+$. Tumor polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, $CD4^+$ or $CD8^+$ T cells that proliferate in response to a tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of the tumor polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

Pharmaceutical Compositions

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable carriers for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will be understood that, if desired, a composition as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as

described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Therefore, in another aspect of the present invention, pharmaceutical compositions are provided comprising one or more of the polynucleotide, polypeptide, antibody, and/or T-cell compositions described herein in combination with a physiologically acceptable carrier. In certain preferred embodiments, the pharmaceutical compositions of the invention comprise immunogenic polynucleotide and/or polypeptide compositions of the invention for use in prophylactic and theraputic vaccine applications. Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Generally, such compositions will comprise one or more polynucleotide and/or polypeptide compositions of the present invention in combination with one or more immunostimulants.

It will be apparent that any of the pharmaceutical compositions described herein can contain pharmaceutically acceptable salts of the polynucleotides and polypeptides of the invention. Such salts can be prepared, for example, from pharmaceutically acceptable non-toxic bases, including organic bases (*e.g.,* salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (*e.g.,* sodium, potassium, lithium, ammonium, calcium and magnesium salts).

In another embodiment, illustrative immunogenic compositions, *e.g.*, vaccine compositions, of the present invention comprise DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the polynucleotide may be administered within any of a variety of delivery systems known to those of ordinary skill in the art. Indeed, numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems 15*:143-198, 1998, and references cited therein. Appropriate polynucleotide expression systems will, of course, contain the necessary regulatory DNA regulatory sequences for expression in a patient (such as a suitable promoter and terminating signal). Alternatively, bacterial delivery systems may involve

the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope.

Therefore, in certain embodiments, polynucleotides encoding immunogenic polypeptides described herein are introduced into suitable mammalian host cells for expression using any of a number of known viral-based systems. In one illustrative embodiment, retroviruses provide a convenient and effective platform for gene delivery systems. A selected nucleotide sequence encoding a polypeptide of the present invention can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to a subject. A number of illustrative retroviral systems have been described (*e.g.*, U.S. Pat. No. 5,219,740; Miller and Rosman (1989) BioTechniques 7:980-990; Miller, A. D. (1990) Human Gene Therapy 1:5-14; Scarpa et al. (1991) Virology 180:849-852; Burns et al. (1993) Proc. Natl. Acad. Sci. USA 90:8033-8037; and Boris-Lawrie and Temin (1993) Cur. Opin. Genet. Develop. 3:102-109.

In addition, a number of illustrative adenovirus-based systems have also been described. Unlike retroviruses which integrate into the host genome, adenoviruses persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham (1986) J. Virol. 57:267-274; Bett et al. (1993) J. Virol. 67:5911-5921; Mittereder et al. (1994) Human Gene Therapy 5:717-729; Seth et al. (1994) J. Virol. 68:933-940; Barr et al. (1994) Gene Therapy 1:51-58; Berkner, K. L. (1988) BioTechniques 6:616-629; and Rich et al. (1993) Human Gene Therapy 4:461-476).

Various adeno-associated virus (AAV) vector systems have also been developed for polynucleotide delivery. AAV vectors can be readily constructed using techniques well known in the art. See, *e.g.*, U.S. Pat. Nos. 5,173,414 and 5,139,941; International Publication Nos. WO 92/01070 and WO 93/03769; Lebkowski et al. (1988) Molec. Cell. Biol. 8:3988-3996; Vincent et al. (1990) Vaccines 90 (Cold Spring Harbor Laboratory Press); Carter, B. J. (1992) Current Opinion in Biotechnology 3:533-539; Muzyczka, N. (1992) Current Topics in Microbiol. and Immunol. 158:97-129;

Kotin, R. M. (1994) Human Gene Therapy 5:793-801; Shelling and Smith (1994) Gene Therapy 1:165-169; and Zhou et al. (1994) J. Exp. Med. 179:1867-1875.

Additional viral vectors useful for delivering the polynucleotides encoding polypeptides of the present invention by gene transfer include those derived from the pox family of viruses, such as vaccinia virus and avian poxvirus. By way of example, vaccinia virus recombinants expressing the novel molecules can be constructed as follows. The DNA encoding a polypeptide is first inserted into an appropriate vector so that it is adjacent to a vaccinia promoter and flanking vaccinia DNA sequences, such as the sequence encoding thymidine kinase (TK). This vector is then used to transfect cells which are simultaneously infected with vaccinia. Homologous recombination serves to insert the vaccinia promoter plus the gene encoding the polypeptide of interest into the viral genome. The resulting TK.sup.(-) recombinant can be selected by culturing the cells in the presence of 5-bromodeoxyuridine and picking viral plaques resistant thereto.

A vaccinia-based infection/transfection system can be conveniently used to provide for inducible, transient expression or coexpression of one or more polypeptides described herein in host cells of an organism. In this particular system, cells are first infected in vitro with a vaccinia virus recombinant that encodes the bacteriophage T7 RNA polymerase. This polymerase displays exquisite specificity in that it only transcribes templates bearing T7 promoters. Following infection, cells are transfected with the polynucleotide or polynucleotides of interest, driven by a T7 promoter. The polymerase expressed in the cytoplasm from the vaccinia virus recombinant transcribes the transfected DNA into RNA which is then translated into polypeptide by the host translational machinery. The method provides for high level, transient, cytoplasmic production of large quantities of RNA and its translation products. See, *e.g.*, Elroy-Stein and Moss, Proc. Natl. Acad. Sci. USA (1990) 87:6743-6747; Fuerst et al. Proc. Natl. Acad. Sci. USA (1986) 83:8122-8126.

Alternatively, avipoxviruses, such as the fowlpox and canarypox viruses, can also be used to deliver the coding sequences of interest. Recombinant avipox viruses, expressing immunogens from mammalian pathogens, are known to confer

protective immunity when administered to non-avian species. The use of an Avipox vector is particularly desirable in human and other mammalian species since members of the Avipox genus can only productively replicate in susceptible avian species and therefore are not infective in mammalian cells. Methods for producing recombinant Avipoxviruses are known in the art and employ genetic recombination, as described above with respect to the production of vaccinia viruses. See, *e.g.*, WO 91/12882; WO 89/03429; and WO 92/03545.

Any of a number of alphavirus vectors can also be used for delivery of polynucleotide compositions of the present invention, such as those vectors described in U.S. Patent Nos. 5,843,723; 6,015,686; 6,008,035 and 6,015,694. Certain vectors based on Venezuelan Equine Encephalitis (VEE) can also be used, illustrative examples of which can be found in U.S. Patent Nos. 5,505,947 and 5,643,576.

Moreover, molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al. J. Biol. Chem. (1993) 268:6866-6869 and Wagner et al. Proc. Natl. Acad. Sci. USA (1992) 89:6099-6103, can also be used for gene delivery under the invention.

Additional illustrative information on these and other known viral-based delivery systems can be found, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA 86*:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld et al., *Science 252*:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA 91*:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA 90*:11498-11502, 1993; Guzman et al., *Circulation 88*:2838-2848, 1993; and Guzman et al., *Cir. Res. 73*:1202-1207, 1993.

In certain embodiments, a polynucleotide may be integrated into the genome of a target cell. This integration may be in a specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the polynucleotide may be stably maintained in the cell as a separate, episomal segment of

DNA. Such polynucleotide segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. The manner in which the expression construct is delivered to a cell and where in the cell the polynucleotide remains is dependent on the type of expression construct employed.

In another embodiment of the invention, a polynucleotide is administered/delivered as "naked" DNA, for example as described in Ulmer et al., *Science 259*:1745-1749, 1993 and reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

In still another embodiment, a composition of the present invention can be delivered via a particle bombardment approach, many of which have been described. In one illustrative example, gas-driven particle acceleration can be achieved with devices such as those manufactured by Powderject Pharmaceuticals PLC (Oxford, UK) and Powderject Vaccines Inc. (Madison, WI), some examples of which are described in U.S. Patent Nos. 5,846,796; 6,010,478; 5,865,796; 5,584,807; and EP Patent No. 0500 799. This approach offers a needle-free delivery approach wherein a dry powder formulation of microscopic particles, such as polynucleotide or polypeptide particles, are accelerated to high speed within a helium gas jet generated by a hand held device, propelling the particles into a target tissue of interest.

In a related embodiment, other devices and methods that may be useful for gas-driven needle-less injection of compositions of the present invention include those provided by Bioject, Inc. (Portland, OR), some examples of which are described in U.S. Patent Nos. 4,790,824; 5,064,413; 5,312,335; 5,383,851; 5,399,163; 5,520,639 and 5,993,412.

According to another embodiment, the pharmaceutical compositions described herein will comprise one or more immunostimulants in addition to the immunogenic polynucleotide, polypeptide, antibody, T-cell and/or APC compositions of this invention. An immunostimulant refers to essentially any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous

antigen. One preferred type of immunostimulant comprises an adjuvant. Many adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Certain adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like growth factors, may also be used as adjuvants.

Within certain embodiments of the invention, the adjuvant composition is preferably one that induces an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (*e.g.*, IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Certain preferred adjuvants for eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt. MPL® adjuvants are available from Corixa Corporation (Seattle, WA; *see*, for example, US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing

oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato et al., *Science 273*:352, 1996. Another preferred adjuvant comprises a saponin, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila Biopharmaceuticals Inc., Framingham, MA); Escin; Digitonin; or *Gypsophila* or *Chenopodium quinoa* saponins . Other preferred formulations include more than one saponin in the adjuvant combinations of the present invention, for example combinations of at least two of the following group comprising QS21, QS7, Quil A, β-escin, or digitonin.

Alternatively the saponin formulations may be combined with vaccine vehicles composed of chitosan or other polycationic polymers, polylactide and polylactide-co-glycolide particles, poly-N-acetyl glucosamine-based polymer matrix, particles composed of polysaccharides or chemically modified polysaccharides, liposomes and lipid-based particles, particles composed of glycerol monoesters, etc. The saponins may also be formulated in the presence of cholesterol to form particulate structures such as liposomes or ISCOMs. Furthermore, the saponins may be formulated together with a polyoxyethylene ether or ester, in either a non-particulate solution or suspension, or in a particulate structure such as a paucilamelar liposome or ISCOM. The saponins may also be formulated with excipients such as Carbopol^R to increase viscosity, or may be formulated in a dry powder form with a powder excipient such as lactose.

In one preferred embodiment, the adjuvant system includes the combination of a monophosphoryl lipid A and a saponin derivative, such as the combination of QS21 and 3D-MPL® adjuvant, as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. Another particularly preferred adjuvant formulation employing QS21, 3D-

MPL® adjuvant and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Another enhanced adjuvant system involves the combination of a CpG-containing oligonucleotide and a saponin derivative particularly the combination of CpG and QS21 is disclosed in WO 00/09159. Preferably the formulation additionally comprises an oil in water emulsion and tocopherol.

Additional illustrative adjuvants for use in the pharmaceutical compositions of the invention include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Enhanzyn®; Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties, and polyoxyethylene ether adjuvants such as those described in WO 99/52549A1.

Other preferred adjuvants include adjuvant molecules of the general formula

(I): $HO(CH_2CH_2O)_n$-A-R,

wherein, n is 1-50, A is a bond or –C(O)-, R is C_{1-50} alkyl or Phenyl C_{1-50} alkyl.

One embodiment of the present invention consists of a vaccine formulation comprising a polyoxyethylene ether of general formula (I), wherein n is between 1 and 50, preferably 4-24, most preferably 9; the R component is C_{1-50}, preferably C_4-C_{20} alkyl and most preferably C_{12} alkyl, and A is a bond. The concentration of the polyoxyethylene ethers should be in the range 0.1-20%, preferably from 0.1-10%, and most preferably in the range 0.1-1%. Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether, polyoxyethylene-9-steoryl ether, polyoxyethylene-8-steoryl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. Polyoxyethylene ethers such as polyoxyethylene lauryl ether are described in the Merck index (12[th] edition: entry 7717). These adjuvant molecules are described in WO

99/52549. The polyoxyethylene ether according to the general formula (I) above may, if desired, be combined with another adjuvant. For example, a preferred adjuvant combination is preferably with CpG as described in the pending UK patent application GB 9820956.2.

According to another embodiment of this invention, an immunogenic composition described herein is delivered to a host via antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.,* matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ,* with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo,* and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med. 4*:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph

nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide of the invention (or portion or other variant thereof) such that the encoded polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a pharmaceutical composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the tumor polypeptide, DNA (naked or within a plasmid vector) or

RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.,* vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.,* a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will typically vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, mucosal, intravenous, intracranial, intraperitoneal, subcutaneous and intramuscular administration.

Carriers for use within such pharmaceutical compositions are biocompatible, and may also be biodegradable. In certain embodiments, the formulation preferably provides a relatively constant level of active component release. In other embodiments, however, a more rapid rate of release immediately upon administration may be desired. The formulation of such compositions is well within the level of ordinary skill in the art using known techniques. Illustrative carriers useful in this regard include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other illustrative delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.,* a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.,* U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

In another illustrative embodiment, biodegradable microspheres (*e.g.,* polylactate polyglycolate) are employed as carriers for the compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763;

5,814,344, 5,407,609 and 5,942,252. Modified hepatitis B core protein carrier systems. such as described in WO/99 40934, and references cited therein, will also be useful for many applications. Another illustrative carrier/delivery system employs a carrier comprising particulate-protein complexes, such as those described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

The pharmaceutical compositions of the invention will often further comprise one or more buffers (*e.g.,* neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.,* glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate.

The pharmaceutical compositions described herein may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are typically sealed in such a way to preserve the sterility and stability of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.,* oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation, is well known in the art, some of which are briefly discussed below for general purposes of illustration.

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they

may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (see, for example, Mathiowitz *et al.*, Nature 1997 Mar 27;386(6623):410-4; Hwang *et al.*, Crit Rev Ther Drug Carrier Syst 1998;15(3):243-84; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451). Tablets, troches, pills, capsules and the like may also contain any of a variety of additional components, for example, a binder, such as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations will contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared is such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration, the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which are further described, for example, in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363. In certain embodiments, solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations generally will contain a preservative to prevent the growth of microorganisms.

Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U. S. Patent 5,466,468). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and/or

by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

In one embodiment, for parenteral administration in an aqueous solution, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. Moreover, for human administration, preparations will of course preferably meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

In another embodiment of the invention, the compositions disclosed herein may be formulated in a neutral or salt form. Illustrative pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be

administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective.

The carriers can further comprise any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described, *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212. Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, J Controlled Release 1998 Mar 2;52(1-2):81-7) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871) are also well-known in the pharmaceutical arts. Likewise, illustrative transmucosal drug delivery in the form of a polytetrafluoroetheylene support matrix is described in U. S. Patent 5,780,045.

In certain embodiments, liposomes, nanocapsules, microparticles, lipid particles, vesicles, and the like, are used for the introduction of the compositions of the present invention into suitable host cells/organisms. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like. Alternatively, compositions of the present invention can be bound, either covalently or non-covalently, to the surface of such carrier vehicles.

The formation and use of liposome and liposome-like preparations as potential drug carriers is generally known to those of skill in the art (see for example, Lasic, Trends Biotechnol 1998 Jul;16(7):307-21; Takakura, Nippon Rinsho 1998

Mar;56(3):691-5; Chandran *et al.*, Indian J Exp Biol. 1997 Aug;35(8):801-9; Margalit, Crit Rev Ther Drug Carrier Syst. 1995;12(2-3):233-61; U.S. Patent 5,567,434; U.S. Patent 5,552,157; U.S. Patent 5,565,213; U.S. Patent 5,738,868 and U.S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally difficult to transfect by other procedures, including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.,* J Biol Chem. 1990 Sep 25;265(27):16337-42; Muller *et al.*, DNA Cell Biol. 1990 Apr;9(3):221-9). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, various drugs, radiotherapeutic agents, enzymes, viruses, transcription factors, allosteric effectors and the like, into a variety of cultured cell lines and animals. Furthermore, he use of liposomes does not appear to be associated with autoimmune responses or unacceptable toxicity after systemic delivery.

In certain embodiments, liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs).

Alternatively, in other embodiments, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (see, for example, Quintanar-Guerrero *et al.*, Drug Dev Ind Pharm. 1998 Dec;24(12):1113-28). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) may be designed using polymers able to be degraded *in vivo*. Such particles can be made as described, for example, by Couvreur *et al.,* Crit Rev Ther Drug Carrier Syst. 1988;5(1):1-20; zur Muhlen *et al.*, Eur J Pharm Biopharm. 1998 Mar;45(2):149-55; Zambaux *et al.* J Controlled Release. 1998 Jan 2;50(1-3):31-40; and U. S. Patent 5,145,684.

Cancer Therapeutic Methods

In further aspects of the present invention, the pharmaceutical compositions described herein may be used for the treatment of cancer, particularly for the immunotherapy of prostate cancer. Within such methods, the pharmaceutical compositions described herein are administered to a patient, typically a warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. As discussed above, administration of the pharmaceutical compositions may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The

polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see*, for example, Cheever et al., *Immunological Reviews 157*:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous,

intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 μg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

Cancer Detection and Diagnostic Compositions, Methods and Kits

In general, a cancer may be detected in a patient based on the presence of one or more prostate tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies)

obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See*, *e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length prostate tumor proteins and polypeptide portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μg, and preferably about 100 ng to about 1 μg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized

on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed

and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1μg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a tumor protein in a biological sample. Within certain methods, a biological sample comprising $CD4^+$ and/or $CD8^+$ T cells isolated from a patient is incubated with a tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (*e.g.*, 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of tumor polypeptide to serve as a control. For $CD4^+$ T cells, activation is preferably detected by evaluating proliferation of the T cells. For $CD8^+$ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a tumor protein of the invention that is at least 10

nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence as disclosed herein. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol., 51*:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the

cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be

present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

EXAMPLE 1

ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES

This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A^+ RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A^+ RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with NotI. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/NotI site of pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis.

The prostate tumor library contained 1.64 x 10^7 independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA library contained 3.3 x 10^6 independent colonies, with 69% of clones having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara *et al.* (*Blood*, *84*:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70 μg) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100 μl of H_2O, heat-denatured and mixed with 100 μl (100 μg) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50 μl) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 μl H_2O to form the driver DNA.

To form the tracer DNA, 10 μg prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 μl H_2O. Tracer DNA was mixed with 15 μl driver DNA and 20 μl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 ^{0}C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 μl H_2O, mixed with 8 μl driver DNA and 20 μl of 2 x hybridization buffer, and subjected to a hybridization at 68

^{0}C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK^{+} (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a prostate tumor specific subtracted cDNA library (referred to as "prostate subtraction 1").

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA), human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified human autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence for F1-12 (also referred to as P504S). This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108. cDNA splice variants of P504S are provided in SEQ ID NO: 600-605.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described above with the normal pancreas cDNA library and with the three most abundant genes

in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1 µg each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to *R. norvegicus* mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to non-human sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S. A cDNA splice variant of P501S is provided in SEQ ID NO: 606.

In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A+ RNA (referred to as "prostate subtraction 2"). The determined cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively. Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

A second subtraction with spike (referred to as "prostate subtraction spike 2") was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17, pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO:73-76, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

Further analysis of the three prostate subtractions described above (prostate subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones, referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and 1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the

isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-4896, provided in SEQ ID NOS: 179-188 and 191-193, respectively, and to the determination of additional partial cDNA sequences for 1I-4810 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of polyA+ RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS: 103 and 104, respectively). Further analysis of the isolated clones led to the

determination of extended cDNA sequences for 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be over-expressed in prostate tumor and normal prostate and expressed at low levels in all other normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously identified ESTs.

Additional, studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 339. Two variant full-length cDNA sequences for P510S are provided in SEQ ID NO: 535 and 536, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 537 and 538, respectively. Additional splice variants of P510S are provided in SEQ ID NO: 598 and 599.

EXAMPLE 2

DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE-SPECIFIC POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the representative prostate-specific polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2 μg of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 ^{0}C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR, β-actin was used as an internal control for each of the tissues examined. First, serial dilutions of the first strand cDNAs were prepared and RT-PCR assays were performed using β-actin specific primers. A dilution was then chosen that enabled the linear range amplification of the β-actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β-actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver, lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin,

small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results thus indicate that F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancrease, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be

over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-expressed in prostate tumor and normal prostate, expressed at lower levels in normal spinal cord, and to be undetectable in all other tissues tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatzis *et al.* (*Proc. Natl. Acad. Sci. USA 95*:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. Subsequent comparison of the sequence of SEQ ID NO: 384 with sequences in the public databases, led to the identification of a full-length cDNA sequence of P1000C (SEQ ID NO: 786), which encodes a 492 amino acid sequence. Analysis of the amino acid sequence using the PSORT II program led to the

identification of a putative transmembrane domain from amino acids 84-100. The cDNA sequence of the open reading frame of P1000C, including the stop codon, is provided in SEQ ID NO: 787, with the open reading frame without the stop codon being provided in SEQ ID NO: 788. The full-length amino acid sequence of P1000C is provided in SEQ ID NO: 789. SEQ ID NO: 790 and 791 represent amino acids 1-100 and 100-492 of P1000C, respectively.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive cytoplasmic staining with rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this polypeptide may be detected selectively in prostate tumors and therefore be useful in the diagnosis of prostate cancer.

EXAMPLE 3

ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' *E. coli* (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

Fifty-nine positive clones were sequenced. Comparison of the DNA sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79 and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

Further studies employing the sequence of SEQ ID NO: 67 as a probe in standard full-length cloning methods, resulted in the isolation of three cDNA sequences which appear to be splice variants of P80 (also known as P704P). These sequences are provided in SEQ ID NO: 620-622.

Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145,

147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine and brain), and activated and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal prostate and prostate tumor, compared to six of twelve other normal tissues tested.

Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes. Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both micro-array technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX_23 was recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of the putative signal sequence. The full-length cDNA sequence for P703P is provided in SEQ ID NO: 524, with the corresponding amino acid sequence being provided in SEQ ID NO: 525.

Using computer algorithms, the following regions of P703P were predicted to represent potential HLA A2-binding CTL epitopes: amino acids 164-172 of SEQ ID NO: 525 (SEQ ID NO: 723); amino acids 160-168 of SEQ ID NO: 525 (SEQ ID NO: 724); amino acids 239-247 of SEQ ID NO: 525 (SEQ ID NO: 725); amino acids 118-126 of SEQ ID NO: 525 (SEQ ID NO: 726); amino acids 112-120 of SEQ ID NO: 525 (SEQ ID NO: 727); amino acids 155-164 of SEQ ID NO: 525 (SEQ ID NO: 728); amino acids 117-126 of SEQ ID NO: 525 (SEQ ID NO: 729); amino acids 164-173 of SEQ ID NO: 525 (SEQ ID NO: 730); amino acids 154-163 of SEQ ID NO:

525 (SEQ ID NO: 731); amino acids 163-172 of SEQ ID NO: 525 (SEQ ID NO: 732); amino acids 58-66 of SEQ ID NO: 525 (SEQ ID NO: 733); and amino acids 59-67 of SEQ ID NO: 525 (SEQ ID NO: 734).

P703P was found to show some homology to previously identified proteases, such as thrombin. The thrombin receptor has been shown to be preferentially expressed in highly metastatic breast carcinoma cells and breast carcinoma biopsy samples. Introduction of thrombin receptor antisense cDNA has been shown to inhibit the invasion of metastatic breast carcinoma cells in culture. Antibodies against thrombin receptor inhibit thrombin receptor activation and thrombin-induced platelet activation. Furthermore, peptides that resemble the receptor's tethered ligand domain inhibit platelet aggregation by thrombin. P703P may play a role in prostate cancer through a protease-activated receptor on the cancer cell or on stromal cells. The potential trypsin-like protease activity of P703P may either activate a protease-activated receptor on the cancer cell membrane to promote tumorgenesis or activate a protease-activated receptor on the adjacent cells (such as stromal cells) to secrete growth factors and/or proteases (such as matrix metalloproteinases) that could promote tumor angiogenesis, invasion and metastasis. P703P may thus promote tumor progression and/or metastasis through the activation of protease-activated receptor. Polypeptides and antibodies that block the P703P-receptor interaction may therefore be usefully employed in the treatment of prostate cancer.

To determine whether P703P expression increases with increased severity of Gleason grade, an indicator of tumor stage, quantitative PCR analysis was performed on prostate tumor samples with a range of Gleason scores from 5 to > 8. The mean level of P703P expression increased with increasing Gleason score, indicating that P703P expression may correlate with increased disease severity.

Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any significant homology to known GenBank sequences. The determined cDNA sequences for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are

provided in SEQ ID NO: 307-311, 313 and 315, respectively. The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold over-expression in prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues. Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

Further studies led to the isolation of an extended cDNA sequence for P712P (SEQ ID NO: 552). The amino acid sequences encoded by 16 predicted open reading frames present within the sequence of SEQ ID NO: 552 are provided in SEQ ID NO: 553-568.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P

were found. Further studies employing the sequence of SEQ ID NO: 334 as a probe in standard full-length cloning methods, resulted in an extended cDNA sequence for P714P. This sequence is provided in SEQ ID NO: 619. This sequence was found to show some homology to the gene that encodes human ribosomal L23A protein.

Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

Further studies on P775P resulted in the isolation of four additional sequences (SEQ ID NO: 473-476) which are all splice variants of the P775P gene. The sequence of SEQ ID NO: 474 was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 477 and 478. The cDNA sequence of SEQ ID NO: 475 was found to contain an ORF which encodes the amino acid sequence of SEQ ID NO: 479. The cDNA sequence of SEQ ID NO: 473 was found to contain four ORFs. The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 480-483. Additional splice variants of P775P are provided in SEQ ID NO: 593-597.

Subsequent studies led to the identification of a genomic region on chromosome 22q11.2, known as the Cat Eye Syndrome region, that contains the five prostate genes P704P, P712P, P774P, P775P and B305D. The relative location of each of these five genes within the genomic region is shown in Fig. 10. This region may therefore be associated with malignant tumors, and other potential tumor genes may be contained within this region. These studies also led to the identification of a potential open reading frame (ORF) for P775P (provided in SEQ ID NO: 533), which encodes the amino acid sequence of SEQ ID NO: 534.

Comparison of the clone of SEQ ID NO: 325 (referred to as P558S) with sequences in the GenBank and GeneSeq DNA databases showed that P558S is identical to the prostate-specific transglutaminase gene, which is known to have two forms. The full-length sequences for the two forms are provided in SEQ ID NO: 630 and 631, with

the corresponding amino acid sequences being provided in SEQ ID NO: 632 and 633, respectively. The cDNA sequence of SEQ ID NO: 631 has a 15 pair base insert, resulting in a 5 amino acid insert in the corresponding amino acid sequence (SEQ ID NO: 633). This insert is not present in the sequence of SEQ ID NO: 630.

Further studies on P768P (SEQ ID NO: 315) led to the identification of the putative full-length open reading frame (ORF). The cDNA sequence of the ORF with stop codon is provided in SEQ ID NO: 764. The cDNA sequence of the ORF without stop codon is provided in SEQ ID NO: 765, with the corresponding amino acid sequence being provided in SEQ ID NO: 766. This sequence was found to show 86% identity to a rat calcium transporter protein, indicating that P768P may represent a human calcium transporter protein. The locations of transmembrane domains within P768P were predicted using the PSORT II computer algorithm. Six transmembrane domains were predicted at amino acid positions 118-134, 172-188, 211-227, 230-246, 282-298 and 348-364. The amino acid sequences of SEQ ID NO: 767-772 represent amino acids 1-134, 135-188, 189-227, 228-246, 247-298 and 299-511 of P768P, respectively.

EXAMPLE 4

SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of

0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

EXAMPLE 5

FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat *norvegicus* cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to *G. gallus* dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most prostate tumors and BPH tissues by a factor of three or greater, with elevated expression

seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be over-expressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349, 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of P544S (SEQ ID NO: 356) which was found to be expressed in small intestine. Of the 26 clones, 11 (SEQ ID NO: 340-349 and 362) were found to show some homology to previously identified sequences. No significant homologies were found to the clones of SEQ ID NO: 350, 351, 353-361, and 363-365.

Comparison of the sequence of SEQ ID NO: 362 with sequences in the GenBank and GeneSeq DNA databases showed that this clone (referred to as P788P) is identical to GeneSeq Accession No. X27262, which encodes a protein found in the GeneSeq protein Accession No. Y00931. The full length cDNA sequence of P788P is provided in SEQ ID NO: 634, with the corresponding predicted amino acid being provided in SEQ ID NO: 635. Subsequently, a full-length cDNA sequence for P788P that contains polymorphisms not found in the sequence of SEQ ID NO: 634, was cloned multiple times by PCR amplification from cDNA prepared from several RNA templates from three individuals. This determined cDNA sequence of this polymorphic variant of P788P is provided in SEQ ID NO: 636, with the corresponding amino acid sequence being provided in SEQ ID NO: 637. The sequence of SEQ ID NO: 637 differs from that of SEQ ID NO: 635 by six amino acid residues. The P788P protein has 7 potential transmembrane domains at the C-terminal portion and is predicted to be a plasma membrane protein with an extracellular N-terminal region.

Further studies on the clone of SEQ ID NO: 352 (referred to as P790P) led to the isolation of the full-length cDNA sequence of SEQ ID NO: 526. The corresponding predicted amino acid is provided in SEQ ID NO: 527. Data from two quantitative PCR experiments indicated that P790P is over-expressed in 11/15 tested prostate tumor samples and is expressed at low levels in spinal cord, with no expression being seen in all other normal samples tested. Data from further PCR experiments and microarray experiments showed over-expression in normal prostate and prostate tumor with little or no expression in other tissues tested. P790P was subsequently found to show significant homology to a previously identified G-protein coupled prostate tissue receptor.

Additional studies on the clone of SEQ ID NO: 354 (referred to as P776P) led to the isolation of an extended cDNA sequence, provided in SEQ ID NO: 569. The determined cDNA sequences of three additional splice variants of P776P are provided in SEQ ID NO: 570-572. The amino acid sequences encoded by two predicted open reading frames (ORFs) contained within SEQ ID NO: 570, one predicted ORF contained within SEQ ID NO: 571, and 11 predicted ORFs contained within SEQ ID NO: 569, are provided in SEQ ID NO: 573-586, respectively. Further studies led to the isolation of the full-length sequence for the clone of SEQ ID NO: 570 (provided in SEQ ID NO: 737). Full-length cloning efforts on the clone of SEQ ID NO: 571 led to the isolation of two sequences (provided in SEQ ID NO: 738 and 739), representing a single clone, that are identical with the exception of a polymorphic insertion/deletion at position 1293. Specifically, the clone of SEQ ID NO: 739 (referred to as clone F1) has a C at position 1293. The clone of SEQ ID NO: 738 (referred to as clone F2) has a single base pair deletion at position 1293. The predicted amino acid sequences encoded by 5 open reading frames located within SEQ ID NO: 737 are provided in SEQ ID NO: 740-744, with the predicted amino acid sequences encoded by the clone of SEQ ID NO: 738 and 739 being provided in SEQ ID NO: 745-750.

Comparison of the cDNA sequences for the clones P767P (SEQ ID NO: 314) and P777P (SEQ ID NO: 350) with sequences in the GenBank human EST database showed that the two clones matched many EST sequences in common,

suggesting that P767P and P777P may represent the same gene. A DNA consensus sequence derived from a DNA sequence alignment of P767P, P777P and multiple EST clones is provided in SEQ ID NO: 587. The amino acid sequences encoded by three putative ORFs located within SEQ ID NO: 587 are provided in SEQ ID NO: 588-590.

The clone of SEQ ID NO: 342 (referred to as P789P) was found to show homology to a previously identified gene. The full length cDNA sequence for P789P and the corresponding amino acid sequence are provided in SEQ ID NO: 735 and 736, respectively.

EXAMPLE 6

PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

Mice expressing the transgene for human HLA A2Kb (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., *Proc. Natl. Acad. Sci. USA 92*:11993-11997, 1995 with the following modifications. Mice were immunized with 100μg of P2S#12 and 120μg of an I-A^b binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at 6 x 10^6 cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL), 2 x 10^{-5} M 2-mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7μg/ml dextran sulfate and 25μg/ml LPS for 3 days). Six days later, cells (5 x 10^5/ml) were restimulated with 2.5 x 10^6/ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells

(Sherman et al, *Science 258*:815-818, 1992) and 3 x 10^6/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x 10^4 cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5 x 10^5 cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2Kb expressing) transduced with P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2Kb molecule.

6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, *et al*, *J. Immunol.*, 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay, test peptides at 100-200 μg/ml were added to cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes,

CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

Mice expressing the transgene for human HLA A2Kb were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA 92*:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5μg of P1S #10 and 120μg of an I-A^b binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single cell suspensions prepared using a nylon mesh. Cells were then resuspended at 6 x 10^6 cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2μg/ml P1S#10 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7μg/ml dextran sulfate and 25μg/ml LPS for 3 days). Six days later cells (5 x 10^5/ml) were restimulated with 2.5 x 10^6/ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and 3 x 10^6/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x 10^4 cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5 x 10^5 cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

EXAMPLE 7

PRIMING OF CTL *IN VIVO* USING NAKED DNA IMMUNIZATION WITH A PROSTATE ANTIGEN

The prostate-specific antigen L1-12, as described above, is also referred to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with 100 μg P501S in the vector VR1012 either intramuscularly or intradermally. The mice were immunized three times, with a two week interval between immunizations. Two weeks after the last immunization, immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL activity was assessed against P501S transduced targets. Two out of 8 mice developed strong anti-P501S CTL responses. These results demonstrate that P501S contains at least one naturally processed HLA-A2-restricted CTL epitope.

EXAMPLE 8

ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE-SPECIFIC POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate tumor polypeptide to recognize human tumor.

Human $CD8^+$ T cells were primed *in vitro* to the P2S-12 peptide (SEQ ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells according to the protocol of Van Tsai et al. (*Critical Reviews in Immunology 18*:65-75, 1998). The resulting $CD8^+$ T cell microcultures were tested for their ability to recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which were transduced to express the P502S gene in a γ-interferon ELISPOT assay (*see* Lalvani et al., *J. Exp. Med. 186*:859-865, 1997). Briefly, titrating numbers of T cells were assayed in duplicate on 10^4 fibroblasts in the presence of 3 μg/ml human β_2-microglobulin and 1 μg/ml P2S-12 peptide or control E75 peptide. In addition, T cells were simultaneously assayed on autologous fibroblasts transduced with the P502S gene or as a control, fibroblasts transduced with HER-2/*neu*. Prior to the assay, the

fibroblasts were treated with 10 ng/ml γ-interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a γ-interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of γ-interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of γ-interferon spots with increasing numbers of T cells on fibroblasts transduced to express the P502S gene but not the HER-2/*neu* gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

EXAMPLE 9

ELICITATION OF PROSTATE ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

This Example illustrates the ability of a prostate-specific antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GMCSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, $CD8^+$ cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles using autologous fibroblasts

retrovirally transduced to express P501S and CD80, CD8+ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501S-transduced fibroblasts. The P501S-specific activity of cell line 3A-1 could be maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxicity assays (^{51}Cr release) and interferon-gamma production (Interferon-gamma Elispot; *see* above and Lalvani et al., *J. Exp. Med. 186*:859-865, 1997). The results of these assays are presented in Figures 6A and 6B.

EXAMPLE 10

IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN THE PROSTATE-SPECIFIC ANTIGEN P703P

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific human CD8+ T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed and P703P-transduced target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2Kb transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of HLA-A2Kb or HLA-A2 transduced target cells expressing P703P.

Initial studies demonstrating that p5 is a naturally processed epitope were done using HLA-A2Kb transgenic mice. HLA-A2Kb transgenic mice were immunized subcutaneously in the footpad with 100 μg of p5 peptide together with 140 μg of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* stimulation. Retrovirally transduced cells expressing the

control antigen P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with 1 ug/ml p5 peptide and cultured with CD8+ T cell enriched PBMC. CTL lines were restimulated on a weekly basis with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures, CTL recognition of p5-pulsed target cells was demonstrated. CTL were additionally shown to recognize human cells transduced to express P703P, demonstrating that p5 is a naturally processed epitope.

Studies identifying a further peptide epitope (referred to as peptide 4) derived from the prostate tumor-specific antigen P703P that is capable of being recognized by CD4 T cells on the surface of cells in the context of HLA class II molecules were carried out as follows. The amino acid sequence for peptide 4 is provided in SEQ ID NO: 638, with the corresponding cDNA sequence being provided in SEQ ID NO: 639.

Twenty 15-mer peptides overlapping by 10 amino acids and derived from the carboxy-terminal fragment of P703P were generated using standard procedures. Dendritic cells (DC) were derived from PBMC of a normal female donor using GM-CSF and IL-4 by standard protocols. CD4 T cells were generated from the same donor as the DC using MACS beads and negative selection. DC were pulsed overnight with pools of the 15-mer peptides, with each peptide at a final concentration of 0.25 microgram/ml. Pulsed DC were washed and plated at 1 x 10^4 cells/well of 96-well V-bottom plates and purified CD4 T cells were added at 1 x 10^5/well. Cultures were supplemented with 60 ng/ml IL-6 and 10 ng/ml IL-12 and incubated at 37 °C. Cultures were restimulated as above on a weekly basis using DC generated and pulsed as above as antigen presenting cells, supplemented with 5 ng/ml IL-7 and 10 u/ml IL-2. Following 4 *in vitro* stimulation cycles, 96 lines (each line corresponding to one well) were tested for specific proliferation and cytokine production in response to the

stimulating pools with an irrelevant pool of peptides derived from mammaglobin being used as a control.

One line (referred to as 1-F9) was identified from pool #1 that demonstrated specific proliferation (measured by 3H proliferation assays) and cytokine production (measured by interferon-gamma ELISA assays) in response to pool #1 of P703P peptides. This line was further tested for specific recognition of the peptide pool, specific recognition of individual peptides in the pool, and in HLA mismatch analyses to identify the relevant restricting allele. Line 1-F9 was found to specifically proliferate and produce interferon-gamma in response to peptide pool #1, and also to peptide 4 (SEQ ID NO: 638). Peptide 4 corresponds to amino acids 126-140 of SEQ ID NO: 327. Peptide titration experiments were conducted to assess the sensitivity of line 1-F9 for the specific peptide. The line was found to specifically respond to peptide 4 at concentrations as low as 0.25 ng/ml, indicating that the T cells are very sensitive and therefore likely to have high affinity for the epitope.

To determine the HLA restriction of the P703P response, a panel of antigen presenting cells (APC) was generated that was partially matched with the donor used to generate the T cells. The APC were pulsed with the peptide and used in proliferation and cytokine assays together with line 1-F9. APC matched with the donor at HLA-DRB0701 and HLA-DQB02 alleles were able to present the peptide to the T cells, indicating that the P703P-specific response is restricted to one of these alleles.

Antibody blocking assays were utilized to determine if the restricting allele was HLA-DR0701 or HLA-DQ02. The anti-HLA-DR blocking antibody L243 or an irrelevant isotype matched IgG2a were added to T cells and APC cultures pulsed with the peptide RMPTVLQCVNVSVVS (SEQ ID NO: 638) at 250 ng/ml. Standard interferon-gamma and proliferation assays were performed. Whereas the control antibody had no effect on the ability of the T cells to recognize peptide-pulsed APC, in both assays the anti-HLA-DR antibody completely blocked the ability of the T cells to specifically recognize peptide-pulsed APC.

To determine if the peptide epitope RMPTVLQCVNVSVVS (SEQ ID NO: 638) was naturally processed, the ability of line 1-F9 to recognize APC pulsed with recombinant P703P protein was examined. For these experiments a number of

recombinant P703P sources were utilized; *E. coli*-derived P703P, Pichia-derived P703P and baculovirus-derived P703P. Irrelevant protein controls used were *E. coli*-derived L3E a lung-specific antigen) and baculovirus-derived mammaglobin. In interferon-gamma ELISA assays, line 1-F9 was able to efficiently recognize both *E. coli* forms of P703P as well as Pichia-derived recombinant P703P, while baculovirus-derived P703P was recognized less efficiently. Subsequent Western blot analysis revealed that the *E coli* and Pichia P703P protein preparations were intact while the baculovirus P703P preparation was approximately 75% degraded. Thus, peptide RMPTVLQCVNVSVVS (SEQ ID NO: 638) from P703P is a naturally processed peptide epitope derived from P703P and presented to T cells in the context of HLA-DRB-0701

In further studies, twenty-four 15-mer peptides overlapping by 10 amino acids and derived from the N-terminal fragment of P703P (corresponding to amino acids 27-154 of SEQ ID NO: 525) were generated by standard procedures and their ability to be recognized by CD4 cells was determined essentially as described above. DC were pulsed overnight with pools of the peptides with each peptide at a final concentration of 10 microgram/ml. A large number of individual CD4 T cell lines (65/480) demonstrated significant proliferation and cytokine release (IFN-gamma) in response to the P703P peptide pools but not to a control peptide pool. The CD4 T cell lines which demonstrated specific activity were restimulated on the appropriate pool of P703P peptides and reassayed on the individual peptides of each pool as well as a peptide dose titration of the pool of peptides in a IFN-gamma release assay and in a proliferation assay.

Sixteen immunogenic peptides were recognized by the T cells from the entire set of peptide antigens tested. The amino acid sequences of these peptides are provided in SEQ ID NO: 656-671, with the corresponding cDNA sequences being provided in SEQ ID NO: 640-655, respectively. In some cases the peptide reactivity of the T cell line could be mapped to a single peptide, however some could be mapped to more than one peptide in each pool. Those CD4 T cell lines that displayed a representative pattern of recognition from each peptide pool with a reasonable affinity for peptide were chosen for further analysis (I-1A, -6A; II-4C, -5E; III-6E, IV-4B, -3F, -9B, -10F, V-5B, -4D, and -10F). These CD4 T cells lines were restimulated on the

appropriate individual peptide and reassayed on autologous DC pulsed with a truncated form of recombinant P703P protein made in *E. coli* (a.a. 96 - 254 of SEQ ID NO: 525), full-length P703P made in the baculovirus expression system, and a fusion between influenza virus NS1 and P703P made in *E. coli*. Of the T cell lines tested, line I-1A recognized specifically the truncated form of P703P (*E. coli*) but no other recombinant form of P703P. This line also recognized the peptide used to elicit the T cells. Line 2-4C recognized the truncated form of P703P (*E. coli*) and the full length form of P703P made in baculovirus, as well as peptide. The remaining T cell lines tested were either peptide-specific only (II-5E, II-6F, IV-4B, IV-3F, IV-9B, IV-10F, V-5B and V-4D) or were non-responsive to any antigen tested (V-10F). These results demonstrate that the peptide sequence RPLLANDLMLIKLDE (SEQ ID NO: 671; corresponding to a.a. 110-124 of SEQ ID NO: 525) recognized by the T cell line I-1A, and the peptide sequences SVSESDTIRSISIAS (SEQ ID NO: 668; corresponding to a.a. 125-139 of SEQ ID NO: 525) and ISIASQCPTAGNSCL (SEQ ID NO: 667; corresponding to a.a. 135-149 of SEQ ID NO: 525) recognized by the T cell line II-4C may be naturally processed epitopes of the P703P protein.

EXAMPLE 11

EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN IN PROSTATE

Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively. In further studies, a splice variant of the cDNA sequence of SEQ ID NO: 366 was isolated which was found to contain an additional guanine residue at position 884 (SEQ ID NO: 530), leading to a frameshift in the open reading frame. The determined DNA sequence of this ORF is

provided in SEQ ID NO: 531. This frameshift generates a protein sequence (provided in SEQ ID NO: 532) of 293 amino acids that contains the C-terminal domain common to the other isoforms of B305D but that differs in the N-terminal region.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach). Using real-time PCR on a panel of prostate tumors, expression of B305D in prostate tumors was shown to increase with increasing Gleason grade, demonstrating that expression of B305D increases as prostate cancer progresses.

EXAMPLE 12

GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION TECHNIQUES WITH THE PROSTATE-SPECIFIC ANTIGEN P501S

Using *in vitro* whole-gene priming with P501S-vaccinia infected DC (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon-γ ELISPOT analysis as described above. Using a panel of HLA-mismatched B-LCL lines transduced with P501S, these CTL lines were shown to be likely restricted to HLAB class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured overnight by the addition of 3 μg/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and priming cultures were initiated

using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S and CD80. Following four stimulation cycles, CD8+ T cell lines were identified that specifically produced interferon-γ when stimulated with P501S and CD80-transduced autologous fibroblasts. A panel of HLA-mismatched B-LCL lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon-γ in an ELISPOT assay, the P501S specific response was shown to be likely restricted by HLA B alleles. These results demonstrate that a CD8+ CTL response to P501S can be elicited.

To identify the epitope(s) recognized, cDNA encoding P501S was fragmented by various restriction digests, and sub-cloned into the retroviral expression vector pBIB-KS. Retroviral supernatants were generated by transfection of the helper packaging line Phoenix-Ampho. Supernatants were then used to transduce Jurkat/A2Kb cells for CTL screening. CTL were screened in IFN-gamma ELISPOT assays against these A2Kb targets transduced with the "library" of P501S fragments. Initial positive fragments P501S/H3 and P501S/F2 were sequenced and found to encode amino acids 106-553 and amino acids 136-547, respectively, of SEQ ID NO: 113. A truncation of H3 was made to encode amino acid residues 106-351 of SEQ ID NO: 113, which was unable to stimulate the CTL, thus localizing the epitope to amino acid residues 351-547. Additional fragments encoding amino acids 1-472 (Fragment A) and amino acids 1-351 (Fragment B) were also constructed. Fragment A but not Fragment B stimulated the CTL thus localizing the epitope to amino acid residues 351-472. Overlapping 20-mer and 18-mer peptides representing this region were tested by pulsing Jurkat/A2Kb cells versus CTL in an IFN-gamma assay. Only peptides P501S-369(20) and P501S-369(18) stimulated the CTL. Nine-mer and 10-mer peptides representing this region were synthesized and similarly tested. Peptide P501S-370 (SEQ ID NO: 539) was the minimal 9-mer giving a strong response. Peptide P501S-376 (SEQ ID NO: 540) also gave a weak response, suggesting that it might represent a cross-reactive epitope.

In subsequent studies, the ability of primary human B cells transduced with P501S to prime MHC class I-restricted, P501S-specific, autologous CD8 T cells was examined. Primary B cells were derived from PBMC of a homozygous HLA-A2 donor by culture in CD40 ligand and IL-4, transduced at high frequency with recombinant P501S in the vector pBIB, and selected with blastocidin-S. For *in vitro* priming, purified CD8+ T cells were cultured with autologous CD40 ligand + IL-4 derived, P501S-transduced B cells in a 96-well microculture format. These CTL microcultures were re-stimulated with P501S-transduced B cells and then assayed for specificity. Following this initial screen, microcultures with significant signal above background were cloned on autologous EBV-transformed B cells (BLCL), also transduced with P501S. Using IFN-gamma ELISPOT for detection, several of these CD8 T cell clones were found to be specific for P501S, as demonstrated by reactivity to BLCL/P501S but not BLCL transduced with control antigen. It was further demonstrated that the anti-P501S CD8 T cell specificity is HLA-A2-restricted. First, antibody blocking experiments with anti-HLA-A,B,C monoclonal antibody (W6.32), anti-HLA-B,C monoclonal antibody (B1.23.2) and a control monoclonal antibody showed that only the anti-HLA-A,B,C antibody blocked recognition of P501S-expressing autologous BLCL. Secondly, the anti-P501S CTL also recognized an HLA-A2 matched, heterologous BLCL transduced with P501S, but not the corresponding EGFP transduced control BLCL.

A naturally processed, CD8, class I-restricted peptide epitope of P501S was identified as follows. Dendritic Cells (DC) were isolated by Percol gradient followed by differential adherence, and cultured for 5 days in the presence of RPMI medium containing 1% human serum, 50ng/ml GM-CSF and 30ng/ml IL-4. Following culture, DC were infected for 24 hours with P501S-expressing adenovirus at an MOI of 10 and matured for an additional 24 hours by the addition of 2ug/ml CD40 ligand. CD8 cells were enriched for by the subtraction of CD4+, CD14+ and CD16+ populations from PBMC with magnetic beads. Priming cultures containing 10,000 P501S-expressing DC and 100,000 CD8+ T cells per well were set up in 96-well V-bottom plates with RPMI containing 10% human serum, 5ng/ml IL-12 and 10ng/ml IL-6. Cultures were stimulated every 7 days using autologous fibroblasts retrovirally

transduced to express P501S and CD80, and were treated with IFN-gamma for 48-72 hours to upregulate MHC Class I expression. 10u/ml IL-2 was added at the time of stimulation and on days 2 and 5 following stimulation. Following 4 stimulation cycles, one P501S-specific CD8+ T cell line (referred to as 2A2) was identified that produced IFN-gamma in response to IFN-gamma-treated P501S/CD80 expressing autologous fibroblasts, but not in response to IFN-gamma-treated P703P/CD80 expressing autologous fibroblasts in a γ-IFN Elispot assay. Line 2A2 was cloned in 96-well plates with 0.5 cell/well or 2 cells/well in the presence of 75,000 PBMC/well, 10,000 B-LCL/well, 30ng/ml OKT3 and 50u/ml IL-2. Twelve clones were isolated that showed strong P501S specificity in response to transduced fibroblasts.

Fluorescence activated cell sorting (FACS) analysis was performed on P501S-specific clones using CD3-, CD4- and CD8-specific antibodies conjugated to PercP, FITC and PE respectively. Consistent with the use of CD8 enriched T cells in the priming cultures, P5401S-specific clones were determined to be CD3+, CD8+ and CD4-.

To identify the relevant P501S epitope recognized by P501S specific CTL, pools of 18-20 mer or 30-mer peptides that spanned the majority of the amino acid sequence of P501S were loaded onto autologous B-LCL and tested in γ-IFN Elispot assays for the ability to stimulate two P501S-specific CTL clones, referred to as 4E5 and 4E7. One pool, composed of five 18-20 mer peptides that spanned amino acids 411-486 of P501S (SEQ ID NO: 113), was found to be recognized by both P501S-specific clones. To identify the specific 18-20 mer peptide recognized by the clones, each of the 18-20 mer peptides that comprised the positive pool were tested individually in γ-IFN Elispot assays for the ability to stimulate the two P501S-specific CTL clones, 4E5 and 4E7. Both 4E5 and 4E7 specifically recognized one 20-mer peptide (SEQ ID NO: 710; cDNA sequence provided in SEQ ID NO: 711) that spanned amino acids 453-472 of P501S. Since the minimal epitope recognized by CD8+ T cells is almost always either a 9 or 10-mer peptide sequence, 10-mer peptides that spanned the entire sequence of SEQ ID NO: 710 were synthesized that differed by 1 amino acid. Each of these 10-mer peptides was tested for the ability to stimulate two P501S-specific clones, (referred to as 1D5 and 1E12). One 10-mer peptide (SEQ ID NO: 712; cDNA sequence provided in

SEQ ID NO: 713) was identified that specifically stimulated the P501S-specific clones. This epitope spans amino acids 463-472 of P501S. This sequence defines a minimal 10-mer epitope from P501S that can be naturally processed and to which CTL responses can be identified in normal PBMC. Thus, this epitope is a candidate for use as a vaccine moiety, and as a therapeutic and/or diagnostic reagent for prostate cancer.

To identify the class I restriction element for the P501S-derived sequence of SEQ ID NO: 712, HLA blocking and mismatch analyses were performed. In γ-IFN Elispot assays, the specific response of clones 4A7 and 4E5 to P501S-transduced autologous fibroblasts was blocked by pre-incubation with 25ug/ml W6/32 (pan-Class I blocking antibody) and B1.23.2 (HLA-B/C blocking antibody). These results demonstrate that the SEQ ID NO: 712-specific response is restricted to an HLA-B or HLA-C allele.

For the HLA mismatch analysis, autologous B-LCL (HLA-A1,A2,B8,B51, Cwl, Cw7) and heterologous B-LCL (HLA-A2,A3,B18,B51,Cw5,Cw14) that share the HLAB51 allele were pulsed for one hour with 20ug/ml of peptide of SEQ ID NO: 712, washed, and tested in γ-IFN Elispot assays for the ability to stimulate clones 4A7 and 4E5. Antibody blocking assays with the B1.23.2 (HLA-B/C blocking antibody) were also performed. SEQ ID NO: 712-specific response was detected using both the autologous (D326) and heterologous (D107) B-LCL, and furthermore the responses were blocked by pre-incubation with 25ug/ml of B1.23.2 HLA-B/C blocking antibody. Together these results demonstrate that the P501S-specific response to the peptide of SEQ ID NO: 712 is restricted to the HLA-B51 class I allele. Molecular cloning and sequence analysis of the HLA-B51 allele from D3326 revealed that the HLA-B51 subtype of D326 is HLA-B51011.

Based on the 10-mer P501S-derived epitope of SEQ ID NO: 712, two 9-mers with the sequences of SEQ ID NO: 714 and 715 were synthesized and tested in Elispot assays for the ability to stimulate two P501S-specific CTL clones derived from line 2A2. The 10-mer peptide of SEQ ID NO: 712, as well as the 9-mer peptide of SEQ ID NO: 715, but not the 9-mer peptide of SEQ ID NO: 714, were capable of stimulating the P501S-specific CTL to produce IFN-gamma. These results demonstrate that the peptide of SEQ ID NO: 715 is a 9-mer P501S-derived epitope recognized by P501S-

specific CTL. The DNA sequence encoding the epitope of SEQ ID NO: 715 is provided in SEQ ID NO: 716.

To identify the class I restricting allele for the P501S-derived peptide of SEQ ID NO: 712 and 715 specific response, each of the HLA B and C alleles were cloned from the donor used in the *in vitro* priming experiment. Sequence analysis indicated that the relevant alleles were HLA-B8, HLA-B51, HLA-Cw01 and HLA-Cw07. Each of these alleles were subcloned into an expression vector and co-transfected together with the P501S gene into VA-13 cells. Transfected VA-13 cells were then tested for the ability to specifically stimulate the P501S-specific CTL in ELISPOT assays. VA-13 cells transfected with P501S and HLA-B51 were capable of stimulating the P501S-specific CTL to secrete gamma-IFN. VA-13 cells transfected with HLA-B51 alone or P501S + the other HLA-alleles were not capable of stimulating the P501S-specific CTL. These results demonstrate that the restricting allele for the P501S-specific response is the HLAB51 allele. Sequence analysis revealed that the subtype of the relevant restricting allele is HLA-B51011.

To determine if the P501S-specific CTL could recognize prostate tumor cells that express P501S, the P501S-positive lines LnCAP and CRL2422 (both expressing "moderate" amounts of P501S mRNA and protein), and PC-3 (expressing low amounts of P501S mRNA and protein), plus the P501S-negative cell line DU-145 were retrovirally transduced with the HLA-B51011 allele that was cloned from the donor used to generate the P501S-specific CTL. HLA-B51011- or EGFP-transduced and selected tumor cells were treated with gamma-interferon and androgen (to upregulate stimulatory functions and P501S, respectively) and used in gamma-interferon Elispot assays with the P501S-specific CTL clones 4E5 and 4E7. Untreated cells were used as a control.

Both 4E5 and 4E7 efficiently and specifically recognized LnCAP and CRL2422 cells that were transduced with the HLA-B51011 allele, but not the same cell lines transduced with EGFP. Additionally, both CTL clones specifically recognized PC-3 cells transduced with HLA-B51011, but not the P501S-negative tumor cell line DU-145. Treatment with gamma-interferon or androgen did not enhance the ability of CTL to recognize tumor cells. These results demonstrate that P501S-specific CTL,

generated by *in vitro* whole gene priming, specifically and efficiently recognize prostate tumor cell lines that express P501S.

A naturally processed CD4 epitope of P501S was identified as follows.

CD4 cells specific for P501S were prepared as described above. A series of 16 overlapping peptides were synthesized that spanned approximately 50% of the amino terminal portion of the P501S gene (amino acids 1- 325 of SEQ ID NO: 113). For priming, peptides were combined into pools of 4 peptides, pulsed at 4 μg/ml onto dendritic cells (DC) for 24 hours, with TNF-alpha. DC were then washed and mixed with negatively selected CD4+ T cells in 96 well U-bottom plates. Cultures were re-stimulated weekly on fresh DC loaded with peptide pools. Following a total of 4 stimulation cycles, cells were rested for an additional week and tested for specificity to APC pulsed with peptide pools using γ-IFN ELISA and proliferation assays. For these assays, adherent monocytes loaded with either the relevant peptide pool at 4ug/ml or an irrelevant peptide at μg/ml were used as APC. T cell lines that demonstrated either specific cytokine secretion or proliferation were then tested for recognition of individual peptides that were present in the pool. T cell lines could be identified from pools A and B that recognized individual peptides from these pools.

From pool A, lines AD9 and AE10 specifically recognized peptide 1 (SEQ ID NO: 719), and line AF5 recognized peptide 39 (SEQ ID NO: 718). From pool B, line BC6 could be identified that recognized peptide 58 (SEQ ID NO: 717). Each of these lines were stimulated on the specific peptide and tested for specific recognition of the peptide in a titration assay as well as cell lysates generated by infection of HEK 293 cells with adenovirus expressing either P501S or an irrelevant antigen. For these assays, APC-adherent monocytes were pulsed with either 10, 1, or 0.1 μg/ml individual P501S peptides, and DC were pulsed overnight with a 1:5 dilution of adenovirally infected cell lysates. Lines AD9, AE10 and AF5 retained significant recognition of the relevant P501S-derived peptides even at 0.1 mg/ml. Furthermore, line AD9 demonstrated significant (8.1 fold stimulation index) specific activity for lysates from adenovirus-P501S infected cells. These results demonstrate that high affinity CD4 T cell lines can be generated toward P501S-derived epitopes, and that at least a subset of these T cells specific for the P501S derived sequence of SEQ ID NO: 719 are specific for an epitope that is naturally processed by human cells. The DNA sequences encoding the amino acid sequences of SEQ ID NO: 717-719 are provided in SEQ ID NO: 720-722, respectively.

To further characterize the P501S-specific activity of AD9, the line was cloned using anti-CD3. Three clones, referred to as 1A1, 1A9 and 1F5, were identified that were specific for the P501S-1 peptide (SEQ ID NO: 719). To determine the HLA restriction allele for the P501S-specific response, each of these clones was tested in class II antibody blocking and HLA mismatch assays using proliferation and gamma-interferon assays. In antibody blocking assays and measuring gamma-interferon production using ELISA assays, the ability of all three clones to recognize peptide pulsed APC was specifically blocked by co-incubation with either a pan-class II blocking antibody or a HLA-DR blocking antibody, but not with a HLA-DQ or an irrelevant antibody. Proliferation assays performed simultaneously with the same cells confirmed these results. These data indicate that the P501S-specific response of the clones is restricted by an HLA-DR allele. Further studies demonstrated that the restricting allele for the P501S-specific response is HLA-DRB1501.

EXAMPLE 13

IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-400) correspond to known sequences, as shown in Table I.

Table I

Summary of Prostate Tumor Antigens

Known Genes	Previously Identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA	P510S	
Ald. 6 Dehyd.	P784P	
L-iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang (23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	
transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		
TEEG		

CGI-82 showed 4.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal prostate, not detected in other normal tissues tested. L-iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal prostate tissues. The expression of this gene in normal tissues was very low. KIAA0122 showed 4.24 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other

normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of normal prostate. It was undetectable in other normal tissues tested. 5566.1 Wang showed 3.31 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 (also referred to as P553S) showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

Subsequent full-length cloning studies on P553S, using standard techniques, revealed that this clone is an incomplete spliced form of P501S. The determined cDNA sequences for four splice variants of P553S are provided in SEQ ID NO: 623-626. An amino acid sequence encoded by SEQ ID NO: 626 is provided in SEQ ID NO: 627. The cDNA sequence of SEQ ID NO: 623 was found to contain two open reading frames (ORFs). The amino acid sequences encoded by these two ORFs are provided in SEQ ID NO: 628 and 629.

EXAMPLE 14

IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate-specific antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatizis et al., *Proc. Natl. Acad. Sci. USA 95*:300-304, 1998). The sequences of EST clones (43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped (aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a "supercluster," resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups: Plus (normal prostate and prostate tumor libraries, and breast cell line libraries, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (libraries from fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

Table II

Prostate cDNA Libraries and ESTs

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones derived from the Plus and Other group libraries only; no expression detected in the Minus group; Type 3- EST clones derived from the Plus, Minus and Other group libraries, but the number of ESTs derived from the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones derived from Plus, Minus and Other group libraries, but the number derived from the Plus group is higher than the number derived from the Minus group. This analysis identified 4,345 breast clusters (*see* Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

Table III

Prostate Cluster Summary

Type	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	85	11
4	673	0
Total	4345	3172

The EST clone inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high levels of tumor vs. normal tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

Clones with an expression ratio greater than 3 (*i.e.,* the level in prostate tumor and normal prostate mRNA was at least three times the level in other normal tissue mRNA) were identified as prostate tumor-specific sequences (Table IV). The sequences of these clones are provided in SEQ ID NO: 401-453, with certain novel sequences shown in SEQ ID NO: 407, 413, 416-419, 422, 426, 427 and 450.

Table IV

Prostate-tumor Specific Clones

SEQ ID NO.	Sequence Designation	Comments
401	22545	previously identified P1000C
402	22547	previously identified P704P
403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel
418	22575	novel
419	22580	novel
420	22581	PAP
421	22582	prostatic secretory protein 94
422	22583	novel
423	22584	prostatic secretory protein 94
424	22585	prostatic secretory protein 94
425	22586	known
426	22587	novel
427	22588	novel
428	22589	PAP
429	22590	known
430	22591	PSA
431	22592	known
432	22593	Previously identified P777P
433	22594	T cell receptor gamma chain
434	22595	Previously identified P705P
435	22596	Previously identified P707P
436	22847	PAP
437	22848	known
438	22849	prostatic secretory protein 57

439	22851	PAP
440	22852	PAP
441	22853	PAP
442	22854	previously identified P509S
443	22855	previously identified P705P
444	22856	previously identified P774P
445	22857	PSA
446	23601	previously identified P777P
447	23602	PSA
448	23605	PSA
449	23606	PSA
450	23612	novel
451	23614	PSA
452	23618	previously identified P1000C
453	23622	previously identified P705P

Further studies on the clone of SEQ ID NO: 407 (also referred to as P1020C) led to the isolation of an extended cDNA sequence provided in SEQ ID NO: 591. This extended cDNA sequence was found to contain an open reading frame that encodes the predicted amino acid sequence of SEQ ID NO: 592. The P1020C cDNA and amino acid sequences were found to show some similarity to the human endogenous retroviral HERV-K pol gene and protein.

EXAMPLE 15

FURTHER IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NO: 454-467. Of these sequences, SEQ ID NO: 459-460 represent novel genes. The others (SEQ ID NO: 454-458 and 461-467) correspond to known sequences. Comparison of the determined

cDNA sequence of SEQ ID NO: 461 with sequences in the Genbank database using the BLAST program revealed homology to the previously identified transmembrane protease serine 2 (TMPRSS2). The full-length cDNA sequence for this clone is provided in SEQ ID NO: 751, with the corresponding amino acid sequence being provided in SEQ ID NO: 752. The cDNA sequence encoding the first 209 amino acids of TMPRSS2 is provided in SEQ ID NO: 753, with the first 209 amino acids being provided in SEQ ID NO: 754.

The sequence of SEQ ID NO: 462 (referred to as P835P) was found to correspond to the previously identified clone FLJ13518 (Accession AK023643; SEQ ID NO: 774), which had no associated open reading frame (ORF). This clone was used to search the Geneseq DNA database and matched a clone previously identified as a G protein-coupled receptor protein (DNA Geneseq Accession A09351; amino acid Geneseq Accession Y92365), that is characterized by the presence of seven transmembrane domains. The sequences of fragments between these domains are provided in SEQ ID NO: 778-785, with SEQ ID NO: 778, 780, 782 and 784 representing extracellular domains and SEQ ID NO: 779, 781, 783 and 785 representing intracellular domains. SEQ ID NO: 778-785 represent amino acids 1-28, 53-61, 83-103, 124-143, 165-201, 226-238, 263-272 and 297-381, respectively, of P835P. The full-length cDNA sequence for P835P is provided in SEQ ID NO: 773. The cDNA sequence of the open reading frame for P835P, including stop codon, is provided in SEQ ID NO: 775, with the open reading frame without stop codon being provided in SEQ ID NO: 776 and the corresponding amino acid sequence being provided in SEQ ID NO: 777.

EXAMPLE 16

FURTHER CHARACTERIZATION OF PROSTATE-SPECIFIC ANTIGEN P710P

This Example describes the full length cloning of P710P.

The prostate cDNA library described above was screened with the P710P fragment described above. One million colonies were plated on LB/Ampicillin plates.

Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic Perkin Elmer/Applied Biosystems Division Sequencer. Four sequences were obtained, and are presented in SEQ ID NO: 468-471. These sequences appear to represent different splice variants of the P710P gene. Subsequent comparison of the cDNA sequences of P710P with those in Genbank revealed homology to the DD3 gene (Genbank accession numbers AF103907 & AF103908). The cDNA sequence of DD3 is provided in SEQ ID NO: 618.

EXAMPLE 17

PROTEIN EXPRESSION OF PROSTATE-SPECIFIC ANTIGENS

This example describes the expression and purification of prostate-specific antigens in *E. coli*, baculovirus, mammalian and yeast cells.

a) Expression of P501S in *E. coli*

Expression of the full-length form of P501S was attempted by first cloning P501S without the leader sequence (amino acids 36-553 of SEQ ID NO: 113) downstream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) in pET17b. Specifically, P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW003 (SEQ ID NO: 486). AW025 is a sense cloning primer that contains a HindIII site. AW003 is an antisense cloning primer that contains an EcoRI site. DNA amplification was performed using 5 μl 10X Pfu buffer, 1 μl 20 mM dNTPs, 1 μl each of the PCR primers at 10 μM concentration, 40 μl water, 1 μl Pfu DNA polymerase (Stratagene, La Jolla, CA) and 1 μl DNA at 100 ng/μl. Denaturation at 95°C was performed for 30 sec, followed by 10 cycles of 95°C for 30 sec, 60°C for 1 min and by 72°C for 3 min. 20 cycles of 95°C for 30 sec, 65°C for 1 min and by 72°C for 3 min, and lastly by 1 cycle of 72°C for 10 min. The PCR product was

cloned to Ra12m/pET17b using HindIII and EcoRI. The sequence of the resulting fusion construct (referred to as Ra12-P501S-F) was confirmed by DNA sequencing.

The fusion construct was transformed into BL21(DE3)pLysE, pLysS and CodonPlus *E. coli* (Stratagene) and grown overnight in LB broth with kanamycin. The resulting culture was induced with IPTG. Protein was transferred to PVDF membrane and blocked with 5% non-fat milk (in PBS-Tween buffer), washed three times and incubated with mouse anti-His tag antibody (Clontech) for 1 hour. The membrane was washed 3 times and probed with HRP-Protein A (Zymed) for 30 min. Finally, the membrane was washed 3 times and developed with ECL (Amersham). No expression was detected by Western blot. Similarly, no expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage (Invitrogen).

An N-terminal fragment of P501S (amino acids 36-325 of SEQ ID NO: 113) was cloned down-stream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 in pET17b as follows. P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW027 (SEQ ID NO: 487). AW027 is an antisense cloning primer that contains an EcoRI site and a stop codon. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The fusion construct (referred to as Ra12-P501S-N) was confirmed by DNA sequencing.

The Ra12-P501S-N fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, essentially as described above. Using Western blot analysis, protein bands were observed at the expected molecular weight of 36 kDa. Some high molecular weight bands were also observed, probably due to aggregation of the recombinant protein. No expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage.

A fusion construct comprising a C-terminal portion of P501S (amino acids 257-553 of SEQ ID NO: 113) located down-stream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) was prepared as follows. P501S

DNA was used to perform PCR using the primers AW026 (SEQ ID NO: 488) and AW003 (SEQ ID NO: 486). AW026 is a sense cloning primer that contains a HindIII site. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The sequence for the fusion construct (referred to as Ra12-P501S-C) was confirmed.

The Ra12-P501S-C fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, as described above. A small amount of protein was detected by Western blot, with some molecular weight aggregates also being observed. Expression was also detected by Western blot when the Ra12-P501S-C fusion was used for expression in BL21CodonPlus induced by CE6 phage.

A fusion construct comprising a fragment of P501S (amino acids 36-298 of SEQ ID NO: 113) located down-stream of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 705) was prepared as follows. P501S DNA was used to perform PCR using the primers AW042 (SEQ ID NO: 706) and AW053 (SEQ ID NO: 707). AW042 is a sense cloning primer that contains a EcoRI site. AW053 is an antisense primer with stop and Xho I sites. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the EcoRI and Xho I sites. The resulting fusion construct (referred to as Ra12-P501S-E2) was expressed in B834 (DE3) pLys S *E. coli* host cells in TB media for 2 h at room temperature. Expressed protein was purified by washing the inclusion bodies and running on a Ni-NTA column. The purified protein stayed soluble in buffer containing 20 mM Tris-HCl (pH 8), 100 mM NaCl, 10 mM β-Me and 5% glycerol. The determined cDNA and amino acid sequences for the expressed fusion protein are provided in SEQ ID NO: 708 and 709, respectfully.

b) Expression of P501S in Baculovirus

The Bac-to-Bac baculovirus expression system (BRL Life Technologies, Inc.) was used to express P501S protein in insect cells. Full-length P501S (SEQ ID NO: 113) was amplified by PCR and cloned into the XbaI site of the donor plasmid pFastBacI. The recombinant bacmid and baculovirus were prepared according to the

manufacturer's instructions. The recombinant baculovirus was amplified in Sf9 cells and the high titer viral stocks were utilized to infect High Five cells (Invitrogen) to make the recombinant protein. The identity of the full-length protein was confirmed by N-terminal sequencing of the recombinant protein and by Western blot analysis (Figure 7). Specifically, 0.6 million High Five cells in 6-well plates were infected with either the unrelated control virus BV/ECD_PD (lane 2), with recombinant baculovirus for P501S at different amounts or MOIs (lanes 4-8), or were uninfected (lane 3). Cell lysates were run on SDS-PAGE under reducing conditions and analyzed by Western blot with the anti-P501S monoclonal antibody P501S-10E3-G4D3 (prepared as described below). Lane 1 is the biotinylated protein molecular weight marker (BioLabs).

The localization of recombinant P501S in the insect cells was investigated as follows. The insect cells overexpressing P501S were fractionated into fractions of nucleus, mitochondria, membrane and cytosol. Equal amounts of protein from each fraction were analyzed by Western blot with a monoclonal antibody against P501S. Due to the scheme of fractionation, both nucleus and mitochondria fractions contain some plasma membrane components. However, the membrane fraction is basically free from mitochondria and nucleus. P501S was found to be present in all fractions that contain the membrane component, suggesting that P501S may be associated with plasma membrane of the insect cells expressing the recombinant protein.

c) Expression of P501S in Mammalian Cells

Full-length P501S (553 amino acids; SEQ ID NO: 113) was cloned into various mammalian expression vectors, including pCEP4 (Invitrogen), pVR1012 (Vical, San Diego, CA) and a modified form of the retroviral vector pBMN, referred to as pBIB. Transfection of P501S/pCEP4 and P501S/pVR1012 into HEK293 fibroblasts was carried out using the Fugene transfection reagent (Boehringer Mannheim). Briefly, 2 ul of Fugene reagent was diluted into 100 ul of serum-free media and incubated at room temperature for 5-10 min. This mixture was added to 1 ug of P501S plasmid DNA, mixed briefly and incubated for 30 minutes at room temperature. The

Fugene/DNA mixture was added to cells and incubated for 24-48 hours. Expression of recombinant P501S in transfected HEK293 fibroblasts was detected by means of Western blot employing a monoclonal antibody to P501S.

Transfection of p501S/pCEP4 into CHO-K cells (American Type Culture Collection, Rockville, MD) was carried out using GenePorter transfection reagent (Gene Therapy Systems, San Diego, CA). Briefly, 15 µl of GenePorter was diluted in 500 µl of serum-free media and incubated at room temperature for 10 min. The GenePorter/media mixture was added to 2 µg of plasmid DNA that was diluted in 500 µl of serum-free media, mixed briefly and incubated for 30 min at room temperature. CHO-K cells were rinsed in PBS to remove serum proteins, and the GenePorter/DNA mix was added and incubated for 5 hours. The transfected cells were then fed an equal volume of 2x media and incubated for 24-48 hours.

FACS analysis of P501S transiently infected CHO-K cells, demonstrated surface expression of P501S. Expression was detected using rabbit polyclonal antisera raised against a P501S peptide, as described below. Flow cytometric analysis was performed using a FaCScan (Becton Dickinson), and the data were analyzed using the Cell Quest program.

d) Expression of P501S in *S. cerevisiae*

P501S was expressed in yeast, directed in membranes, using the yeast α prepro signal sequence. The natural signal sequence and first lumenal domain of P501S was deleted in order to conserve the natural positioning of the expressed P501S protein.

Specifically, the α prepro signal sequence of *S. cerevisiae* linked to amino acids 55-553 of SEQ ID NO: 113 with a His tag tail was cloned into the plasmid pRIT15068 with the CUP1 promoter and transfected into *S. cerevisiae* strain Y1790. The Y1790 strain is Leu+ and His-. Expression of protein was induced by addition of either 500 µM or 250 µM of $CuSO_4$ at 30 °C in minimal medium supplemented with histidine. Cells were harvested 24 hours after induction. Extracts were prepared by growing cells to a concentration of OD600 5.0 in 50 mM citrate phosphate buffer (pH 4.0) plus 130 mM NaCl supplemented with protease inhibitors. Cells were disrupted

using glass beads and centrifuged for 20 min at 15,000 g. The recombinant protein was found to be 100% pellet associated.

Expression of the recombinant protein (molecular weight 63 kD) was demonstrated by Western blot analysis, using the anti-P501S monoclonal antibody 10E-D4-G3 described below. The amino acid sequence of the expressed protein is provided in SEQ ID NO: 792.

Fermentation processes for the production of the α prepro-P501S-His tag recombinant protein in *S. cerevisiae* (strain Y1790 – CUP1 inducible promoter) were evaluated as follows. One hundred μl of a master seed containing 2.5 x 10^8 cells/ml of transformed *S. cerevisiae* Y1790 were spread on FSC004AA solid medium. The composition of the FSC004AA medium is as follows: glucose 10 g/l; $Na_2MoO_4.2H_2O$ 0.0002 g/l; folic acid 0.000064 g/l; KH_2PO_4 1 g/l; $MnSO_4.H_2O$ 0.0004 g/l; Inositol 0.064 g/l; $MgSO_4.7H_2O$ 0.5 g/l; H_3BO_3 0.0005 g/l; Pyridoxine 0.008 g/l; $CaCl_2.2H_2O$ 0.1 g/l; KI 0.0001 g/l; Thiamine 0.008 g/l; NaCl 0.1 g/l; $CoCl_2.6H_2O$ 0.00009 g/l; Niacin 0.000032 g/l; $FeCl_3.6H_2O$ 0.0002 g/l; Riboflavin 0.000016 g/l; Panthotenate Ca 0.008 g/l; $CuSO_4.5H_2O$ 0.00004 g/l; Biotin 0.000064 g/l; para-aminobenzoic acid 0.000016 g/l; $ZnSO_4.7H_2O$ 0.0004 g/l; $(NH_4)_2SO_4$ 5 g/l; agar 18 g/l; Histidine 0.1 g/l.

Two plates were incubated for 26 h at 30 °C. These solid pre-cultures were harvested in 5 ml of liquid medium FSC007AA and 0.5 ml (or 9.3 x 10^7 cells) of this suspension was used to inoculate 2 liquid pre-cultures.

The composition of the FSC007AA medium is as follows: Glucose 10 g/l; $Na_2MoO_4.2H_2O$ 0.0002 g/l; folic acid 0.000064 g/l; KH_2PO_4 1 g/l; $MnSO_4.H_2O$ 0.0004 g/l; Inositol 0.064 g/l; $MgSO_4.7H_2O$ 0.5 g/l; H_3BO_3 0.0005 g/l; Pyridoxine 0.008 g/l; $CaCl_2.2H_2O$ 0.1 g/l; KI 0.0001 g/l; Thiamine 0.008 g/l; NaCl 0.1 g/l; $CoCl_2.6H_2O$ 0.00009 g/l; Niacine 0.000032 g/l; $FeCl_3.6H_2O$ 0.0002 g/l; Riboflavin 0.000016 g/l; Panthotenate Ca 0.008 g/l; $CuSO_4.5H_2O$ 0.00004 g/l; Biotin 0.000064 g/l; para-aminobenzoic acid 0.000016 g/l; $ZnSO_4.7H_2O$ 0.0004 g/l; $(NH_4)_2SO_4$ 5 g/l; Histidine 0.1 g/l.

<u>These pre-cultures were run for 20 hours in 2L flasks containing 400 ml of medium FSC007AA in order to obtain an OD of 1.8. The other characteristics of these pre-cultures are as follows: pH 2.8; glucose 2.3 g/L; ethanol 3.4 g/L.</u>

The best timing for liquid pre-cultures for strain Y1790 was determined in preliminary experiments. Liquid pre-cultures containing 400 ml of medium and inoculated with various volumes of Master Seed (0.25, 0.5, 1 or 2 ml) were monitored in order to identify the best inoculum size and timing. Glucose, ethanol, pH, OD and cell number (determined by flow cytometry) were followed between 16 and 23 hours of culture. Glucose exhaustion and maximal biomass were obtained after 20 hour incubation with 0.5 inoculum. These conditions were adopted for transferring the pre-culture into fermentation.

In total, 800ml of pre-culture were used to inoculate a 20 L fermenter containing 5L of medium FSC002AA. Three ml of irradiated antifoam were added before inoculation. The composition of the FSC002AA medium is as follows: $(NH_4)_2SO_4$ 6.4 g/l; $Na_2MoO_4.2H_2O$ 2.05 mg/l; folic acid 0.54 mg/l; KH_2PO_4 8.25 g/l; $MnSO_4.H_2O$ 4.1 mg/l; inositol 540 mg/; $MgSO_4.7H_2O$ 4.69 g/l; H_3BO_3 5.17 m/l; pyridoxine 68 mg/l; $CaCl_2.2H_2O$ 0.92 g/l; KI 1.03 mg/l; thiamine 68 mg/l; NaCl 0.06g/l; $CoCl_2.6H_2O$ 0.92 mg/l; Niacine 0.27 mg/l; HCl 1 ml/l; $FeCl_3.6H_2O$ 9.92 mg/l; Riboflavin 0.13 mg/l; $CuSO_4.5H_2O$ 0.41 mg/l; Glucose 0.14 g/l; Panthotenate Ca 68 mg/l; $ZnSO_4.7H_2O$ 4.1 mg/l; Biotin 0.54 mg/l; para-aminobenzoic acid 0.13 mg/l; Histidine 0.3 g/l

The carbon source (glucose) was supplemented by a continuous feeding of FFB004AA medium. The composition of the FFB004AA medium is as follows: glucose 350 g/l; $Na_2MoO_4.2H_2O$ 5.15 mg/l; folic acid 1.36 mg/l; KH_2PO_4 20.6 g/l; $MnSO_4.H_2O$ 10.3 mg/l; inositol 1350 mg/l; $MgSO_4.7H_2O$ 11.7 g/l; H_3BO_3 12.9 m/l; pyridoxine 170 mg/l; $CaCl_2.2H_2O$ 2.35 g/l; KI 2.6 mg/l; thiamine 170 g/l; NaCl 0.15 g/l; $CoCl_2.6H_2O$ 2.3 mg/l; niacine 0.67 mg/l; HCl 2.5 ml/l; $FeCl_3.6H_2O$ 24.8 mg/l; riboflavin; 0.33 mg/l; $CuSO_4.5H_2O$ 1.03 mg/l; biotin 1.36 mg/l; panthotenate Ca 170 mg/l; $ZnSO_4.7H_2O$ 10.3 mg/l; para-aminobenzoic acid: 0.33 mg/l; histidine 5.35 g/l.

The residual glucose concentration was maintained very low (□50 mg/L) in order to minimize ethanol production by fermentation. This was achieved by limiting the development of the microorganism using a limited glucose feed rate. The Standard biomass content (OD 80-90) was reached in fermentation after 44 hour growth phase.

CUP1 promoter was then induced by adding 500µM $CuSO_4$ in order to

produce P501S antigen. $CuSO_4$ addition was followed by ethanol accumulation (up to 6 g/L), and the glucose feeding rate was then reduced in order to consume the ethanol. The copper available for the microorganism was monitored by testing Cu ion concentration in the broth supernatant using a spectrophotometric copper assay (DETC method). The fermentation was then supplemented by $CuSO_4$ throughout the induction phase in order to maintain its concentration between 150 and 250 μM in the supernatant. The biomass reached an OD of 100 at the end of induction. Cells were harvested after 8 hours of induction.

Cell homogenate was prepared and analysed by SDS-PAGE and Western Blot using standard protocols. A major protein band with the expected molecular weight of 62KD was detected by Western blot using anti-P501S monoclonal antibodies. Western blot analysis also showed that the major 62KD band was progressively produced from 30 minutes of induction on, and reached a maximum after 3 hours. No more antigen seemed to be produced between 3 and 12 hours of induction.

The number of passages through a French Press necessary to extract all the antigen from the cells was evaluated. One, three and five passages were tested and total cell lysates, supernatants and pellets of cell lysates were analysed by Western blot. Three passages through a French Press were sufficient to completely extract the antigen. The antigen was present in the insoluble fraction.

e) <u>Expression of P703P in Baculovirus</u>

The cDNA for full-length P703P-DE5 (SEQ ID NO: 326), together with several flanking restriction sites, was obtained by digesting the plasmid pCDNA703 with restriction endonucleases Xba I and Hind III. The resulting restriction fragment (approx. 800 base pairs) was ligated into the transfer plasmid pFastBacI which was digested with the same restriction enzymes. The sequence of the insert was confirmed by DNA sequencing. The recombinant transfer plasmid pFBP703 was used to make recombinant bacmid DNA and baculovirus using the Bac-To-Bac Baculovirus expression system (BRL Life Technologies). High Five cells were infected with the recombinant virus BVP703, as described above, to obtain recombinant P703P protein.

e) Expression of P788P in *E. Coli*

A truncated, N-terminal portion, of P788P (residues 1-644 of SEQ ID NO: 777; referred to as P788P-N) fused with a C-terminal 6xHis Tag was expressed in *E. coli* as follows. P788P cDNA was amplified using the primers AW080 and AW081 (SEQ ID NO: 672 and 673). AW080 is a sense cloning primer with an NdeI site. AW081 is an antisense cloning primer with a XhoI site. The PCR-amplified P788P, as well as the vector pCRX1, were digested with NdeI and XhoI. Vector and insert were ligated and transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. P788P-N clone #6 was confirmed to be identical to the designed construct. The expression construct P788P-N #6/pCRX1 was transformed into *E. coli* BL21 CodonPlus-RIL competent cells. After induction, most of the cells grew well, achieving OD600 of greater than 2.0 after 3 hr. Coomassie stained SDS-PAGE showed an over-expressed band at about 75 kD. Western blot analysis using a 6xHisTag antibody confirmed the band was P788P-N. The determined cDNA sequence for P788P-N is provided in SEQ ID NO: 674, with the corresponding amino acid sequence being provided in SEQ ID NO: 675.

f) Expression of P510S in *E. Coli*

The P510S protein has 9 potential transmembrane domains and is predicted to be located at the plasma membrane. The C-terminal protein of this protein, as well as the predicted third extracellular domain of P510S were expressed in *E. coli* as follows.

The expression construct referred to as Ra12-P501S-C was designed to have a 6 HisTag at the N-terminal enc, followed by the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 676) and then the C-terminal portion of P510S (amino residues 1176-1261 of SEQ ID NO: 538). Full-length P510S was used to amplify the P510S-C fragment by PCR using the primers AW056 and AW057 (SEQ ID NO: 677 and 678, respectively). AW056 is a sense cloning primer with an EcoRI site. AW057 is an antisense primer with stop and XhoI sites. The amplified P501S fragment and Ra12/pCRX1 were digested with EcoRI and XhoI and then purified. The insert and

vector were ligated together and transformed into NovaBlue. Colonies were randomly screened for insert and sequences. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. A mini-induction screen was performed to optimize the expression conditions. After induction the cells grew well, achieving OD 600 nm greater than 2.0 after 3 hours. Coomassie stain SDS-PAGE showed a highly over-expressed band at approx. 30 kD. Though this is higher than the expected molecular weight, western blot analysis was positive, showing this band to be the His tag-containing protein. The optimized culture conditions are as follows. Dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2xYT (with kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2xYT. Allow to grow at 37 °C until OD600 = 0.6. Take an aliquot out as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3 sample, spin down cells and store at -80 °C. The determined cDNA and amino acid sequences for the Ra12-P510S-C construct are provided in SEQ ID NO: 679 and 682, respectively.

The expression construct P510S-C was designed to have a 5' added start codon and a glycine (GGA) codon and then the P510S C terminal fragment followed by the in frame 6x histidine tag and stop codon from the pET28b vector. The cloning strategy is similar to that used for Ra12-P510S-C, except that the PCR primers employed were those shown in SEQ ID NO: 685 and 686, respectively and the NcoI/XhoI cut in pET28b was used. The primer of SEQ ID NO: 685 created a 5' NcoI site and added a start codon. The antisense primer of SEQ ID NO: 686 creates a XhoI site on P510S C terminal fragment. Clones were confirmed by sequencing. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. An OD600 of greater than 2.0 was obtained 30 hours after induction. Coomassie stained SDS-PAGE showed an over-expressed band at about 11 kD. Western blot analysis confirmed that the band was P510S-C, as did N-terminal protein sequencing. The optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT (+ kanamycin and chloramphenicol) at a ratio of 25 mL culture to 1 liter 2x YT, and allow to grow at

37 °C until an OD 600 of about 0.5 is reached. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequences for the P510S-C construct are shown in SEQ ID NO: 680 and 683, respectively.

The predicted third extracellular domain of P510S (P510S-E3; residues 328-676 of SEQ ID NO: 538) was expressed in *E. coli* as follows. The P510S fragment was amplified by PCR using the primers shown in SEQ ID NO: 687 and 688. The primer of SEQ ID NO: 687 is a sense primer with an NdeI site for use in ligating into pPDM. The primer of SEQ ID NO: 688 is an antisense primer with an added XhoI site for use in ligating into pPDM. The resulting fragment was cloned to pPDM at the NdeI and XhoI sites. Clones were confirmed by sequencing. For protein expression, the clone ws transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. After induction, an OD600 of greater than 2.0 was achieved after 3 hours. Coomassie stained SDS-PAGE showed an over-expressed band at about 39 kD, and N-terminal sequencing confirmed the N-terminal to be that of P510S-E3. Optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT (kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2x YT. Allow to grow at 37 °C until OD 600 equals 0.6. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3 sample, spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequences for the P501S-E3 construct are provided in SEQ ID NO: 681 and 684, respectively.

g) Expression of P775S in *E. Coli*

The antigen P775P contains multiple open reading frames (ORF). The third ORF, encoding the protein of SEQ ID NO: 483, has the best emotif score. An expression fusion construct containing the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 676) and P775P-ORF3 with an N-terminal 6x HisTag was prepared as follows. P775P-ORF3 was amplified using the sense PCR primers of SEQ ID NO: 689 and the anti-sense PCR primer of SEQ ID NO: 690. The PCR amplified fragment of P775P and

Ra12/pCRX1 were digested with the restriction enzymes EcoRI and XhoI. Vector and insert were ligated and then transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. A clone having the desired sequence was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. Two hours after induction, the cell density peaked at OD600 of approximately 1.8. Coomassie stained SDS-PAGE showed an over-expressed band at about 31 kD. Western blot using 6x HisTag antibody confirmed that the band was Ra12-P775P-ORF3. The determined cDNA and amino acid sequences for the fusion construct are provided in SEQ ID NO: 691 and 692, respectively.

H) Expression of a P703P His tag fusion protein in E. coli

The cDNA for the coding region of P703P was prepared by PCR using the primers of SEQ ID NO: 693 and 694. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P703P are provided in SEQ ID NO: 695 and 696, respectively.

I) Expression of a P705P His tag fusion protein in E. coli

The cDNA for the coding region of P705P was prepared by PCR using the primers of SEQ ID NO: 697 and 698. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S and BL21 (DE3) CodonPlus expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P705P are provided in SEQ ID NO: 699 and 700, respectively.

J) EXPRESSION OF A P711P HIS TAG FUSION PROTEIN IN E. COLI

The cDNA for the coding region of P711P was prepared by PCR using the primers of SEQ ID NO: 701 and 702. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S and BL21 (DE3) CodonPlus expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P711P are provided in SEQ ID NO: 703 and 704, respectively.

EXAMPLE 18

PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST PROSTATE-SPECIFIC POLYPEPTIDES

a) Preparation and Characterization of Polyclonal Antibodies against P703P, P504S and P509S

Polyclonal antibodies against P703P, P504S and P509S were prepared as follows.

Each prostate tumor antigen expressed in an *E. coli* recombinant expression system was grown overnight in LB broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning, 10 ml of the overnight culture was added to 500 ml to 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nm) of the culture reached 0.4-0.6, the cells were induced with IPTG (1 mM). Four hours after induction with IPTG, the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty ml of lysis buffer was added to the cell pellets and vortexed. To break open the *E. coli* cells, this mixture was then run

through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0, 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM Tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification.

As a final purification step, a strong anion exchange resin such as HiPrepQ (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off the column with a increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. The proteins were then vialed after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

Four hundred micrograms of each prostate antigen was combined with 100 micrograms of muramyldipeptide (MDP). Every four weeks rabbits were boosted with 100 micrograms mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animal was bled. Sera was generated by incubating the blood at 4°C for 12-4 hours followed by centrifugation.

Ninety-six well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) of recombinant protein at 4 °C for 20 hours. 250 microliters of BSA blocking buffer was added to the wells and incubated at room

temperature for 2 hours. Plates were washed 6 times with PBS/0.01% Tween. Rabbit sera was diluted in PBS. Fifty microliters of diluted sera was added to each well and incubated at room temperature for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at room temperature for 30 min. Plates were again washed as described above and 100 microliters of TMB microwell peroxidase substrate was added to each well. Following a 15 min incubation in the dark at room temperature, the colorimetric reaction was stopped with 100 microliters of 1N H_2SO_4 and read immediately at 450 nm. All polyclonal antibodies showed immunoreactivity to the appropriate antigen.

b) Preparation and Characterization of Antibodies against P501S

A murine monoclonal antibody directed against the carboxy-terminus of the prostate-specific antigen P501S was prepared as follows.

A truncated fragment of P501S (amino acids 355-526 of SEQ ID NO: 113) was generated and cloned into the pET28b vector (Novagen) and expressed in *E. coli* as a thioredoxin fusion protein with a histidine tag. The trx-P501S fusion protein was purified by nickel chromatography, digested with thrombin to remove the trx fragment and further purified by an acid precipitation procedure followed by reverse phase HPLC.

Mice were immunized with truncated P501S protein. Serum bleeds from mice that potentially contained anti-P501S polyclonal sera were tested for P501S-specific reactivity using ELISA assays with purified P501S and trx-P501S proteins. Serum bleeds that appeared to react specifically with P501S were then screened for P501S reactivity by Western analysis. Mice that contained a P501S-specific antibody component were sacrificed and spleen cells were used to generate anti-P501S antibody producing hybridomas using standard techniques. Hybridoma supernatants were tested for P501S-specific reactivity initially by ELISA, and subsequently by FACS analysis of reactivity with P501S transduced cells. Based on these results, a monoclonal hybridoma referred to as 10E3 was chosen for further subcloning. A number of subclones were

generated, tested for specific reactivity to P501S using ELISA and typed for IgG isotype. The results of this analysis are shown below in Table V. Of the 16 subclones tested, the monoclonal antibody 10E3-G4-D3 was selected for further study.

Table V

Isotype analysis of murine anti-P501S monoclonal antibodies

Hybridoma clone	Isotype	Estimated [Ig] in supernatant (μg/ml)
4D11	IgG1	14.6
1G1	IgG1	0.6
4F6	IgG1	72
4H5	IgG1	13.8
4H5-E12	IgG1	10.7
4H5-EH2	IgG1	9.2
4H5-H2-A10	IgG1	10
4H5-H2-A3	IgG1	12.8
4H5-H2-A10-G6	IgG1	13.6
4H5-H2-B11	IgG1	12.3
10E3	IgG2a	3.4
10E3-D4	IgG2a	3.8
10E3-D4-G3	IgG2a	9.5
10E3-D4-G6	IgG2a	10.4
10E3-E7	IgG2a	6.5
8H12	IgG2a	0.6

The specificity of 10E3-G4-D3 for P501S was examined by FACS analysis. Specifically, cells were fixed (2% formaldehyde, 10 minutes), permeabilized (0.1% saponin, 10 minutes) and stained with 10E3-G4-D3 at 0.5 – 1 μg/ml, followed by incubation with a secondary, FITC-conjugated goat anti-mouse Ig antibody (Pharmingen, San Diego, CA). Cells were then analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. For analysis of infected cells, B-LCL were infected with a vaccinia vector that expresses P501S. To demonstrate specificity in these assays, B-LCL transduced with a different antigen (P703P) and uninfected B-LCL vectors were utilized. 10E3-G4-D3 was shown to bind with P501S-transduced B-

LCL and also with P501S-infected B-LCL, but not with either uninfected cells or P703P-transduced cells.

To determine whether the epitope recognized by 10E3-G4-D3 was found on the surface or in an intracellular compartment of cells, B-LCL were transduced with P501S or HLA-B8'as a control antigen and either fixed and permeabilized as described above or directly stained with 10E3-G4-D3 and analyzed as above. Specific recognition of P501S by 10E3-G4-D3 was found to require permeabilization, suggesting that the epitope recognized by this antibody is intracellular.

The reactivity of 10E3-G4-D3 with the three prostate tumor cell lines Lncap, PC-3 and DU-145, which are known to express high, medium and very low levels of P501S, respectively, was examined by permeabilizing the cells and treating them as described above. Higher reactivity of 10E3-G4-D3 was seen with Lncap than with PC-3, which in turn showed higher reactivity that DU-145. These results are in agreement with the real time PCR and demonstrate that the antibody specifically recognizes P501S in these tumor cell lines and that the epitope recognized in prostate tumor cell lines is also intracellular.

Specificity of 10E3-G4-D3 for P501S was also demonstrated by Western blot analysis. Lysates from the prostate tumor cell lines Lncap, DU-145 and PC-3, from P501S-transiently transfected HEK293 cells, and from non-transfected HEK293 cells were generated. Western blot analysis of these lysates with 10E3-G4-D3 revealed a 46 kDa immunoreactive band in Lncap, PC-3 and P501S-transfected HEK cells, but not in DU-145 cells or non-transfected HEK293 cells. P501S mRNA expression is consistent with these results since semi-quantitative PCR analysis revealed that P501S mRNA is expressed in Lncap, to a lesser but detectable level in PC-3 and not at all in DU-145 cells. Bacterially expressed and purified recombinant P501S (referred to as P501SStr2) was recognized by 10E3-G4-D3 (24 kDa), as was full-length P501S that was transiently expressed in HEK293 cells using either the expression vector VR1012 or pCEP4. Although the predicted molecular weight of P501S is 60.5 kDa, both transfected and "native" P501S run at a slightly lower mobility due to its hydrophobic nature.

Immunohistochemical analysis was performed on prostate tumor and a panel of normal tissue sections (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder, ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). Tissue samples were fixed in formalin solution for 24 hours and embedded in paraffin before being sliced into 10 micron sections. Tissue sections were permeabilized and incubated with 10E3-G4-D3 antibody for 1 hr. HRP-labeled anti-mouse followed by incubation with DAB chromogen was used to visualize P501S immunoreactivity. P501S was found to be highly expressed in both normal prostate and prostate tumor tissue but was not detected in any of the other tissues tested.

To identify the epitope recognized by 10E3-G4-D3, an epitope mapping approach was pursued. A series of 13 overlapping 20-21 mers (5 amino acid overlap; SEQ ID NO: 489-501) was synthesized that spanned the fragment of P501S used to generate 10E3-G4-D3. Flat bottom 96 well microtiter plates were coated with either the peptides or the P501S fragment used to immunize mice, at 1 microgram/ml for 2 hours at 37 °C. Wells were then aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature, and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified antibody 10E3-G4-D3 was added at 2 fold dilutions (1000 ng – 16 ng) in PBST and incubated for 30 minutes at room temperature. This was followed by washing 6 times with PBST and subsequently incubating with HRP-conjugated donkey anti-mouse IgG (H+L)Affinipure F(ab') fragment (Jackson Immunoresearch, West Grove, PA) at 1:20000 for 30 minutes. Plates were then washed and incubated for 15 minutes in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 8, reactivity was seen with the peptide of SEQ ID NO: 496 (corresponding to amino acids 439-459 of P501S) and with the P501S fragment but not with the remaining peptides, demonstrating that the epitope recognized by 10E3-G4-D3 is localized to amino acids 439-459 of SEQ ID NO: 113.

In order to further evaluate the tissue specificity of P501S, multi-array immunohistochemical analysis was performed on approximately 4700 different human tissues encompassing all the major normal organs as well as neoplasias derived from

these tissues. Sixty-five of these human tissue samples were of prostate origin. Tissue sections 0.6 mm in diameter were formalin-fixed and paraffin embedded. Samples were pretreated with HIER using 10 mM citrate buffer pH 6.0 and boiling for 10 min. Sections were stained with 10E3-G4-D3 and P501S immunoreactivity was visualized with HRP. All the 65 prostate tissues samples (5 normal, 55 untreated prostate tumors, 5 hormone refractory prostate tumors) were positive, showing distinct perinuclear staining. All other tissues examined were negative for P501S expression.

c) Preparation and Characterization of Antibodies against P503S

A fragment of P503S (amino acids 113-241 of SEQ ID NO: 114) was expressed and purified from bacteria essentially as described above for P501S and used to immunize both rabbits and mice. Mouse monoclonal antibodies were isolated using standard hybridoma technology as described above. Rabbit monoclonal antibodies were isolated using Selected Lymphocyte Antibody Method (SLAM) technology at Immgenics Pharmaceuticals (Vancouver, BC, Canada). Table VI, below, lists the monoclonal antibodies that were developed against P503S.

Table VI

Antibody	Species
20D4	Rabbit
JA1	Rabbit
1A4	Mouse
1C3	Mouse
1C9	Mouse
1D12	Mouse
2A11	Mouse
2H9	Mouse
4H7	Mouse
8A8	Mouse
8D10	Mouse
9C12	Mouse
6D12	Mouse

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 20D4 and JA1 were determined and are provided in SEQ ID NO: 502 and 503, respectively.

In order to better define the epitope binding region of each of the antibodies, a series of overlapping peptides were generated that span amino acids 109-213 of SEQ ID NO: 114. These peptides were used to epitope map the anti-P503S monoclonal antibodies by ELISA as follows. The recombinant fragment of P503S that was employed as the immunogen was used as a positive control. Ninety-six well microtiter plates were coated with either peptide or recombinant antigen at 20 ng/well overnight at 4 °C. Plates were aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature then washed in PBS containing 0.1% Tween 20 (PBST). Purified rabbit monoclonal antibodies diluted in PBST were added to the wells and incubated for 30 min at room temperature. This was followed by washing 6 times with PBST and incubation with Protein-A HRP conjugate at a 1:2000 dilution for a further 30 min. Plates were washed six times in PBST and incubated with tetramethylbenzidine (TMB) substrate for a further 15 min. The reaction was stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using at ELISA plate reader. ELISA with the mouse monoclonal antibodies was performed with supernatants from tissue culture run neat in the assay.

All of the antibodies bound to the recombinant P503S fragment, with the exception of the negative control SP2 supernatant. 20D4, JA1 and 1D12 bound strictly to peptide #2101 (SEQ ID NO: 504), which corresponds to amino acids 151-169 of SEQ ID NO: 114. 1C3 bound to peptide #2102 (SEQ ID NO: 505), which corresponds to amino acids 165-184 of SEQ ID NO: 114. 9C12 bound to peptide #2099 (SEQ ID NO: 522), which corresponds to amino acids 120-139 of SEQ ID NO: 114. The other antibodies bind to regions that were not examined in these studies.

Subsequent to epitope mapping, the antibodies were tested by FACS analysis on a cell line that stably expressed P503S to confirm that the antibodies bind to cell surface epitopes. Cells stably transfected with a control plasmid were employed as

a negative control. Cells were stained live with no fixative. 0.5 ug of anti-P503S monoclonal antibody was added and cells were incubated on ice for 30 min before being washed twice and incubated with a FITC-labelled goat anti-rabbit or mouse secondary antibody for 20 min. After being washed twice, cells were analyzed with an Excalibur fluorescent activated cell sorter. The monoclonal antibodies 1C3, 1D12, 9C12, 20D4 and JA1, but not 8D3, were found to bind to a cell surface epitope of P503S.

In order to determine which tissues express P503S, immunohistochemical analysis was performed, essentially as described above, on a panel of normal tissues (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder, ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). HRP-labeled anti-mouse or anti-rabbit antibody followed by incubation with TMB was used to visualize P503S immunoreactivity. P503S was found to be highly expressed in prostate tissue, with lower levels of expression being observed in cervix, colon, ileum and kidney, and no expression being observed in adrenal, breast, duodenum, gall bladder, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis.

Western blot analysis was used to characterize anti-P503S monoclonal antibody specificity. SDS-PAGE was performed on recombinant (rec) P503S expressed in and purified from bacteria and on lysates from HEK293 cells transfected with full length P503S. Protein was transferred to nitrocellulose and then Western blotted with each of the anti-P503S monoclonal antibodies (20D4, JA1, 1D12, 6D12 and 9C12) at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to either a goat anti-mouse monoclonal antibody or to protein A-sepharose. The monoclonal antibody 20D4 detected the appropriate molecular weight 14 kDa recombinant P503S (amino acids 113-241) and the 23.5 kDa species in the HEK293 cell lysates transfected with full length P503S. Other anti-P503S monoclonal antibodies displayed similar specificity by Western blot.

d) Preparation and Characterization of Antibodies against P703P

Rabbits were immunized with either a truncated (P703Ptr1; SEQ ID NO: 172) or full-length mature form (P703Pfl; SEQ ID NO: 523) of recombinant P703P

protein was expressed in and purified from bacteria as described above. Affinity purified polyclonal antibody was generated using immunogen P703Pfl or P703Ptr1 attached to a solid support. Rabbit monoclonal antibodies were isolated using SLAM technology at Immgenics Pharmaceuticals. Table VII below lists both the polyclonal and monoclonal antibodies that were generated against P703P.

Table VII

Antibody	Immunogen	Species/type
Aff. Purif. P703P (truncated); #2594	P703Ptrl	Rabbit polyclonal
Aff. Purif. P703P (full length); #9245	P703Pfl	Rabbit polyclonal
2D4	P703Ptrl	Rabbit monoclonal
8H2	P703Ptrl	Rabbit monoclonal
7H8	P703Ptrl	Rabbit monoclonal

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 8H2, 7H8 and 2D4 were determined and are provided in SEQ ID NO: 506-508, respectively.

Epitope mapping studies were performed as described above. Monoclonal antibodies 2D4 and 7H8 were found to specifically bind to the peptides of SEQ ID NO: 509 (corresponding to amino acids 145-159 of SEQ ID NO: 172) and SEQ ID NO: 510 (corresponding to amino acids 11-25 of SEQ ID NO: 172), respectively. The polyclonal antibody 2594 was found to bind to the peptides of SEQ ID NO: 511-514, with the polyclonal antibody 9427 binding to the peptides of SEQ ID NO: 515-517.

The specificity of the anti-P703P antibodies was determined by Western blot analysis as follows. SDS-PAGE was performed on (1) bacterially expressed recombinant antigen; (2) lysates of HEK293 cells and Ltk-/- cells either untransfected or transfected with a plasmid expressing full length P703P; and (3) supernatant isolated from these cell cultures. Protein was transferred to nitrocellulose and then Western blotted using the anti-P703P polyclonal antibody #2594 at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to an anti-rabbit antibody. A 35 kDa immunoreactive band could be observed with

recombinant P703P. Recombinant P703P runs at a slightly higher molecular weight since it is epitope tagged. In lysates and supernatants from cells transfected with full length P703P, a 30 kDa band corresponding to P703P was observed. To assure specificity, lysates from HEK293 cells stably transfected with a control plasmid were also tested and were negative for P703P expression. Other anti-P703P antibodies showed similar results.

Immunohistochemical studies were performed as described above, using anti-P703P monoclonal antibody. P703P was found to be expressed at high levels in normal prostate and prostate tumor tissue but was not detectable in all other tissues tested (breast tumor, lung tumor and normal kidney).

e) Preparation and Characterization of Antibodies against P504S

Full-length P504S (SEQ ID NO: 108) was expressed and purified from bacteria essentially as described above for P501S and employed to raise rabbit monoclonal antibodies using Selected Lymphocyte Antibody Method (SLAM) technology at Immgenics Pharmaceuticals (Vancouver, BC, Canada). The anti-P504S monoclonal antibody 13H4 was shown by Western blot to bind to both expressed recombinant P504S and to native P504S in tumor cells.

Immunohistochemical studies using 13H4 to assess P504S expression in various prostate tissues were performed as described above. A total of 104 cases, including 65 cases of radical prostatectomies with prostate cancer (PC), 26 cases of prostate biopsies and 13 cases of benign prostate hyperplasia (BPH), were stained with the anti-P504S monoclonal antibody 13H4. P504S showed strongly cytoplasmic granular staining in 64/65 (98.5%) of PCs in prostatectomies and 26/26 (100%) of PCs in prostatic biopsies. P504S was stained strongly and diffusely in carcinomas (4+ in 91.2% of cases of PC; 3+ in 5.5%; 2+ in 2.2% and 1+ in 1.1%) and high grade prostatic intraepithelial neoplasia (4+ in all cases). The expression of P504S did not vary with Gleason score. Only 17/91 (18.7%) of cases of NP/BPH around PC and 2/13 (15.4%) of BPH cases were focally (1+, no 2+ to 4+ in all cases) and weakly positive for P504S in large glands. Expression of P504S was not found in small atrophic glands, postatrophic hyperplasia, basal cell hyperplasia and transitional cell metaplasia in either biopsies or

prostatectomies. P504S was thus found to be over-expressed in all Gleason scores of prostate cancer (98.5 to 100% of sensitivity) and exhibited only focal positivities in large normal glands in 19/104 of cases (82.3% of specificity). These findings indicate that P504S may be usefully employed for the diagnosis of prostate cancer.

EXAMPLE 19

CHARACTERIZATION OF CELL SURFACE EXPRESSION AND CHROMOSOME LOCALIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

This example describes studies demonstrating that the prostate-specific antigen P501S is expressed on the surface of cells, together with studies to determine the probable chromosomal location of P501S.

The protein P501S (SEQ ID NO: 113) is predicted to have 11 transmembrane domains. Based on the discovery that the epitope recognized by the anti-P501S monoclonal antibody 10E3-G4-D3 (described above in Example 17) is intracellular, it was predicted that following transmembrane determinants would allow the prediction of extracellular domains of P501S. Fig. 9 is a schematic representation of the P501S protein showing the predicted location of the transmembrane domains and the intracellular epitope described in Example 17. Underlined sequence represents the predicted transmembrane domains, bold sequence represents the predicted extracellular domains, and italicized sequence represents the predicted intracellular domains. Sequence that is both bold and underlined represents sequence employed to generate polyclonal rabbit serum. The location of the transmembrane domains was predicted using HHMTOP as described by Tusnady and Simon (Principles Governing Amino Acid Composition of Integral Membrane Proteins: Applications to Topology Prediction, *J. Mol. Biol. 283*:489-506, 1998).

Based on Fig. 9, the P501S domain flanked by the transmembrane domains corresponding to amino acids 274-295 and 323-342 is predicted to be extracellular. The peptide of SEQ ID NO: 518 corresponds to amino acids 306-320 of P501S and lies in the predicted extracellular domain. The peptide of SEQ ID NO: 519,

which is identical to the peptide of SEQ ID NO: 518 with the exception of the substitution of the histidine with an asparginine, was synthesized as described above. A Cys-Gly was added to the C-terminus of the peptide to facilitate conjugation to the carrier protein. Cleavage of the peptide from the solid support was carried out using the following cleavage mixture: trifluoroacetic acid:ethanediol:thioanisol:water:phenol (40:1:2:2:3). After cleaving for two hours, the peptide was precipitated in cold ether. The peptide pellet was then dissolved in 10% v/v acetic acid and lyophilized prior to purification by C18 reverse phase hplc. A gradient of 5-60% acetonitrile (containing 0.05% TFA) in water (containing 0.05% TFA) was used to elute the peptide. The purity of the peptide was verified by hplc and mass spectrometry, and was determined to be >95%. The purified peptide was used to generate rabbit polyclonal antisera as described above.

Surface expression of P501S was examined by FACS analysis. Cells were stained with the polyclonal anti-P501S peptide serum at 10 μg/ml, washed, incubated with a secondary FITC-conjugated goat anti-rabbit Ig antibody (ICN), washed and analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. To demonstrate specificity in these assays, B-LCL transduced with an irrelevant antigen (P703P) or nontransduced were stained in parallel. For FACS analysis of prostate tumor cell lines, Lncap, PC-3 and DU-145 were utilized. Prostate tumor cell lines were dissociated from tissue culture plates using cell dissociation medium and stained as above. All samples were treated with propidium iodide (PI) prior to FACS analysis, and data was obtained from PI-excluding (*i.e.,* intact and non-permeabilized) cells. The rabbit polyclonal serum generated against the peptide of SEQ ID NO: 519 was shown to specifically recognize the surface of cells transduced to express P501S, demonstrating that the epitope recognized by the polyclonal serum is extracellular.

To determine biochemically if P501S is expressed on the cell surface, peripheral membranes from Lncap cells were isolated and subjected to Western blot analysis. Specifically, Lncap cells were lysed using a dounce homogenizer in 5 ml of homogenization buffer (250 mM sucrose, 10 mM HEPES, 1mM EDTA, pH 8.0, 1

complete protease inhibitor tablet (Boehringer Mannheim)). Lysate samples were spun at 1000 g for 5 min at 4 °C. The supernatant was then spun at 8000g for 10 min at 4 °C. Supernatant from the 8000g spin was recovered and subjected to a 100,000g spin for 30 min at 4 °C to recover peripheral membrane. Samples were then separated by SDS-PAGE and Western blotted with the mouse monoclonal antibody 10E3-G4-D3 (described above in Example 17) using conditions described above. Recombinant purified P501S, as well as HEK293 cells transfected with and over-expressing P501S were included as positive controls for P501S detection. LCL cell lysate was included as a negative control. P501S could be detected in Lncap total cell lysate, the 8000g (internal membrane) fraction and also in the 100,000g (plasma membrane) fraction. These results indicate that P501S is expressed at, and localizes to, the peripheral membrane.

To demonstrate that the rabbit polyclonal antiserum generated to the peptide of SEQ ID NO: 519 specifically recognizes this peptide as well as the corresponding native peptide of SEQ ID NO: 518, ELISA analyses were performed. For these analyses, flat-bottomed 96 well microtiter plates were coated with either the peptide of SEQ ID NO: 519, the longer peptide of SEQ ID NO: 520 that spans the entire predicted extracellular domain, the peptide of SEQ ID NO: 521 which represents the epitope recognized by the P501S-specific antibody 10E3-G4-D3, or a P501S fragment (corresponding to amino acids 355-526 of SEQ ID NO: 113) that does not include the immunizing peptide sequence, at 1 μg/ml for 2 hours at 37 °C. Wells were aspirated, blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified anti-P501S polyclonal rabbit serum was added at 2 fold dilutions (1000 ng - 125 ng) in PBST and incubated for 30 min at room temperature. This was followed by washing 6 times with PBST and incubating with HRP-conjugated goat anti-rabbit IgG (H+L) Affinipure F(ab') fragment at 1:20000 for 30 min. Plates were then washed and incubated for 15 min in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 11, the anti-P501S polyclonal rabbit serum specifically recognized the

peptide of SEQ ID NO: 519 used in the immunization as well as the longer peptide of SEQ ID NO: 520, but did not recognize the irrelevant P501S-derived peptides and fragments.

In further studies, rabbits were immunized with peptides derived from the P501S sequence and predicted to be either extracellular or intracellular, as shown in Fig. 9. Polyclonal rabbit sera were isolated and polyclonal antibodies in the serum were purified, as described above. To determine specific reactivity with P501S, FACS analysis was employed, utilizing either B-LCL transduced with P501S or the irrelevant antigen P703P, of B-LCL infected with vaccinia virus-expressing P501S. For surface expression, dead and non-intact cells were excluded from the analysis as described above. For intracellular staining, cells were fixed and permeabilized as described above. Rabbit polyclonal serum generated against the peptide of SEQ ID NO: 548, which corresponds to amino acids 181-198 of P501S, was found to recognize a surface epitope of P501S. Rabbit polyclonal serum generated against the peptide SEQ ID NO: 551, which corresponds to amino acids 543-553 of P501S, was found to recognize an epitope that was either potentially extracellular or intracellular since in different experiments intact or permeabilized cells were recognized by the polyclonal sera. Based on similar deductive reasoning, the sequences of SEQ ID NO: 541-547, 549 and 550, which correspond to amino acids 109-122, 539-553, 509-520, 37-54, 342-359, 295-323, 217-274, 143-160 and 75-88, respectively, of P501S, can be considered to be potential surface epitopes of P501S recognized by antibodies.

In further studies, mouse monoclonal antibodies were raised against amino acids 296 to 322 to P501S, which are predicted to be in an extracellular domain. A/J mice were immunized with P501S/adenovirus, followed by subsequent boosts with an *E. coli* recombinant protein, referred to as P501N, that contains amino acids 296 to 322 of P501S, and with peptide 296-322 (SEQ ID NO: 755) coupled with KLH. The mice were subsequently used for splenic B cell fusions to generate anti-peptide hybridomas. The resulting 3 clones, referred to as 4F4 (IgG1,kappa), 4G5 (IgG2a,kappa) and 9B9 (IgG1,kappa), were grown for antibody production. The 4G5 mAb was purified by passing the supernatant over a Protein A-sepharose column,

followed by antibody elution using 0.2M glycine, pH 2.3. Purified antibody was neutralized by the addition of 1M Tris, pH 8, and buffer exchanged into PBS.

For ELISA analysis, 96 well plates were coated with P501S peptide 296-322 (referred to as P501-long), an irrelevant P775 peptide, P501S-N, P501TR2, P501S-long-KLH, P501S peptide 306-319 (referred to as P501-short)-KLH, or the irrelevant peptide 2073-KLH, all at a concentration of 2 ug/ml and allowed to incubate for 60 minutes at 37 °C. After coating, plates were washed 5X with PBS + 0.1% Tween and then blocked with PBS, 0.5% BSA, 0.4% Tween20 for 2 hours at room temperature. Following the addition of supernatants or purified mAb, the plates were incubated for 60 minutes at room temperature. Plates were washed as above and donkey anti-mouse IgHRP-linked secondary antibody was added and incubated for 30 minutes at room temperature, followed by a final washing as above. TMB peroxidase substrate was added and incubated 15 minutes at room temperature in the dark. The reaction was stopped by the addition of 1N H_2SO_4 and the OD was read at 450 nM. All three hybrid clones secreted mAb that recognized peptide 296-322 and the recombinant protein P501N.

For FACS analysis, HEK293 cells were transiently transfected with a P501S/VR1012 expression constructs using Fugene 6 reagent. After 2 days of culture, cells were harvested and washed, then incubated with purified 4G5 mAb for 30 minutes on ice. After several washes in PBS, 0.5% BSA, 0.01% azide, goat anti-mouse Ig-FITC was added to the cells and incubated for 30 minutes on ice. Cells were washed and resuspended in wash buffer including 1% propidium iodide and subjected to FACS analysis. The FACS analysis confirmed that amino acids 296-322 of P501S are in an extracellular domain and are cell surface expressed.

The chromosomal location of P501S was determined using the GeneBridge 4 Radiation Hybrid panel (Research Genetics). The PCR primers of SEQ ID NO: 528 and 529 were employed in PCR with DNA pools from the hybrid panel according to the manufacturer's directions. After 38 cycles of amplification, the reaction products were separated on a 1.2% agarose gel, and the results were analyzed through the Whitehead Institute/MIT Center for Genome Research web server

(http://www-genome.wi.mit.edu/cgi-bin/contig/rhmapper.pl) to determine the probable chromosomal location. Using this approach, P501S was mapped to the long arm of chromosome 1 at WI-9641 between q32 and q42. This region of chromosome 1 has been linked to prostate cancer susceptibility in hereditary prostate cancer (Smith *et al. Science 274*:1371-1374, 1996 and Berthon *et al. Am. J. Hum. Genet. 62*:1416-1424, 1998). These results suggest that P501S may play a role in prostate cancer malignancy.

EXAMPLE 20

REGULATION OF EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

Steroid (androgen) hormone modulation is a common treatment modality in prostate cancer. The expression of a number of prostate tissue-specific antigens have previously been demonstrated to respond to androgen. The responsiveness of the prostate-specific antigen P501S to androgen treatment was examined in a tissue culture system as follows.

Cells from the prostate tumor cell line LNCaP were plated at 1.5×10^6 cells/T75 flask (for RNA isolation) or 3×10^5 cells/well of a 6-well plate (for FACS analysis) and grown overnight in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum (BRL Life Technologies, Gaithersburg, MD). Cell culture was continued for an additional 72 hours in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum, with 1 nM of the synthetic androgen Methyltrienolone (R1881; New England Nuclear) added at various time points. Cells were then harvested for RNA isolation and FACS analysis at 0, 1, 2, 4, 8, 16, 24, 28 and 72-hours post androgen addition. FACS analysis was performed using the anti-P501S antibody 10E3-G4-D3 and permeabilized cells.

For Northern analysis, 5-10 micrograms of total RNA was run on a formaldehyde denaturing gel, transferred to Hybond-N nylon membrane (Amersham Pharmacia Biotech, Piscataway, NJ), cross-linked and stained with methylene blue. The filter was then prehybridized with Church's Buffer (250 mM Na_2HPO_4, 70 mM H_3PO_4, 1 mM EDTA, 1% SDS, 1% BSA in pH 7.2) at 65 °C for 1 hour. P501S DNA was

labeled with 32P using High Prime random-primed DNA labeling kit (Boehringer Mannheim). Unincorporated label was removed using MicroSpin S300-HR columns (Amersham Pharmacia Biotech). The RNA filter was then hybridized with fresh Church's Buffer containing labeled cDNA overnight, washed with 1X SCP (0.1 M NaCl, 0.03 M $Na_2HPO_4.7H_2O$, 0.001 M Na_2EDTA), 1% sarkosyl (n-lauroylsarcosine) and exposed to X-ray film.

Using both FACS and Northern analysis, P501S message and protein levels were found in increase in response to androgen treatment.

EXAMPLE 20

PREPARATION OF FUSION PROTEINS OF PROSTATE-SPECIFIC ANTIGENS

The example describes the preparation of a fusion protein of the prostate-specific antigen P703P and a truncated form of the known prostate antigen PSA. The truncated form of PSA has a 21 amino acid deletion around the active serine site. The expression construct for the fusion protein also has a restriction site at 3' end, immediately prior to the termination codon, to aid in adding cDNA for additional antigens.

The full-length cDNA for PSA was obtained by RT-PCR from a pool of RNA from human prostate tumor tissues using the primers of SEQ ID NO: 607 and 608, and cloned in the vector pCR-Blunt II-TOPO. The resulting cDNA was employed as a template to make two different fragments of PSA by PCR with two sets of primers (SEQ ID NO: 609 and 610; and SEQ ID NO: 611 and 612). The PCR products having the expected size were used as templates to make truncated forms of PSA by PCR with the primers of SEQ ID NO: 611 and 613, which generated PSA (delta 208-218 in amino acids). The cDNA for the mature form of P703P with a 6X histidine tag at the 5' end, was prepared by PCR with P703P and the primers of SEQ ID NO: 614 and 615. The cDNA for the fusion of P703P with the truncated form of PSA (referred to as FOPP) was then obtained by PCR using the modified P703P cDNA and the truncated form of PSA cDNA as templates and the primers of SEQ ID NO: 614 and 615. The FOPP

cDNA was cloned into the NdeI site and XhoI site of the expression vector pCRX1, and confirmed by DNA sequencing. The determined cDNA sequence for the fusion construct FOPP is provided in SEQ ID NO: 616, with the amino acid sequence being provided in SEQ ID NO: 617.

The fusion FOPP was expressed as a single recombinant protein in *E. coli* as follows. The expression plasmid pCRX1FOPP was transformed into the *E. coli* strain BL21-CodonPlus RIL. The transformant was shown to express FOPP protein upon induction with 1 mM IPTG. The culture of the corresponding expression clone was inoculated into 25 ml LB broth containing 50 ug/ml kanamycin and 34 ug/ml chloramphenicol, grown at 37 °C to OD600 of about 1, and stored at 4 °C overnight. The culture was diluted into 1 liter of TB LB containing 50 ug/ml kanamycin and 34 ug/ml chloramphenicol, and grown at 37 °C to OD600 of 0.4. IPTG was added to a final concentration of 1 mM, and the culture was incubated at 30 °C for 3 hours. The cells were pelleted by centrifugation at 5,000 RPM for 8 min. To purify the protein, the cell pellet was suspended in 25 ml of 10 mM Tris-Cl pH 8.0, 2mM PMSF, complete protease inhibitor and 15 ug lysozyme. The cells were lysed at 4 °C for 30 minutes, sonicated several times and the lysate centrifuged for 30 minutes at 10,000 x g. The precipitate, which contained the inclusion body, was washed twice with 10 mM Tris-Cl pH 8.0 and 1% CHAPS. The inclusion body was dissolved in 40 ml of 10 mM Tris-Cl pH 8.0, 100 mM sodium phosphate and 8 M urea. The solution was bound to 8 ml Ni-NTA (Qiagen) for one hour at room temperature. The mixture was poured into a 25 ml column and washed with 50 ml of 10 mM Tris-Cl pH 6.3, 100 mM sodium phosphate, 0.5% DOC and 8M urea. The bound protein was eluted with 350 mM imidazole, 10 mM Tris-Cl pH 8.0, 100 mM sodium phosphate and 8 M urea. The fractions containing FOPP proteins were combined and dialyzed extensively against 10 mM Tris-Cl pH 4.6, aliquoted and stored at - 70 °C.

EXAMPLE 21

REAL-TIME PCR CHARACTERIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S IN PERIPHERAL BLOOD OF PROSTATE CANCER PATIENTS

Circulating epithelial cells were isolated from fresh blood of normal individuals and metastatic prostate cancer patients, mRNA isolated and cDNA prepared using real-time PCR procedures. Real-time PCR was performed with the Taqman^{TM} procedure using both gene specific primers and probes to determine the levels of gene expression.

Epithelial cells were enriched from blood samples using an immunomagnetic bead separation method (Dynal A.S., Oslo, Norway). Isolated cells were lysed and the magnetic beads removed. The lysate was then processed for poly A+ mRNA isolation using magnetic beads coated with Oligo(dT)25. After washing the beads in buffer, bead/poly A+ RNA samples were suspended in 10 mM Tris HCl pH 8.0 and subjected to reversed transcription. The resulting cDNA was subjected to real-time PCR using gene specific primers. Beta-actin content was also determined and used for normalization. Samples with P501S copies greater than the mean of the normal samples + 3 standard deviations were considered positive. Real time PCR on blood samples was performed using the Taqman^{TM} procedure but extending to 50 cycles using forward and reverse primers and probes specific for P501S. Of the eight samples tested, 6 were positive for P501S and β-actin signal. The remaining 2 samples had no detectable β-actin or P501S. No P501S signal was observed in the four normal blood samples tested.

EXAMPLE 22

EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGENS P703P AND P501S IN SCID MOUSE-PASSAGED PROSTATE TUMORS

When considering the effectiveness of antigens in the treatment of prostate cancer, the continued presence of the antigens in tumors during androgen

ablation therapy is important. The presence of the prostate-specific antigens P703P and P501S in prostate tumor samples grown in SCID mice in the presence of testosterone was evaluated as follows.

Two prostate tumors that had metastasized to the bone were removed from patients, implanted into SCID mice and grown in the presence of testosterone. Tumors were evaluated for mRNA expression of P703P, P501S and PSA using quantitative real time PCR with the SYBR green assay method. Expression of P703P and P501S in a prostate tumor was used as a positive control and the absence in normal intestine and normal heart as negative controls. In both cases, the specific mRNA was present in late passage tumors. Since the bone metastases were grown in the presence of testosterone, this implies that the presence of these genes would not be lost during androgen ablation therapy.

EXAMPLE 23

ANTI-P503S MONOCLONAL ANTIBODY INHIBITS TUMOR GROWTH *IN VIVO*

The ability of the anti-P503S monoclonal antibody 20D4 to suppress tumor formation in mice was examined as follows.

Ten SCID mice were injected subcutaneously with HEK293 cells that expressed P503S. Five mice received 150 micrograms of 20D4 intravenously at day 0 (time of tumor cell injection), day 5 and day 9. Tumor size was measured for 50 days. Of the five animals that received no 20D4, three formed detectable tumors after about 2 weeks which continued to enlarge throughout the study. In contrast, none of the five mice that received 20D4 formed tumors. These results demonstrate that the anti-P503S Mab 20D4 displays potent anti-tumor activity *in vivo*.

EXAMPLE 24

CHARACTERIZATION OF A T CELL RECEPTOR CLONE FROM A P501S-SPECIFIC T CELL CLONE

T cells have a limited lifespan. However, cloning of T cell receptor (TCR) chains and subsequent transfer essentially enables infinite propagation of the T

cell specificity. Cloning of tumor-antigen TCR chains allows the transfer of the specificity into T cells isolated from patients that share the TCR MHC-restricting allele. Such T cells could then be expanded and used in adoptive transfer settings to introduce the tumor antigen specificity into patients carrying tumors that express the antigen. T cell receptor alpha and beta chains from a CD8 T cell clone specific for the prostate-specific antigen P501S were isolated and sequenced as follows.

Total mRNA from 2 x 10^6 cells from CTL clone 4E5 (described above in Example 12) was isolated using Trizol reagent and cDNA was synthesized. To determine Va and Vb sequences in this clone, a panel of Va and Vb subtype-specific primers was synthesized and used in RT-PCR reactions with cDNA generated from each of the clones. The RT-PCR reactions demonstrated that each of the clones expressed a common Vb sequence that corresponded to the Vb7 subfamily. Futhermore, using cDNA generated from the clone, the Va sequence expressed was determined to be Va6. To clone the full TCR alpha and beta chains from clone 4E5, primers were designed that spanned the initiator and terminator-coding TCR nucleotides. The primers were as follows: TCR Valpha-6 5'(sense): GGATCC---GCCGCCACC—ATGTCACTTTCTAGCCTGCT (SEQ ID NO: 756) BamHI site Kozak TCR alpha sequence TCR alpha 3' (antisense): GTCGAC---TCAGCTGGACCACAGCCGCAG (SEQ ID NO: 757) SalI site TCR alpha constant sequence TCR Vbeta-7. 5'(sense): GGATCC---GCCGCCACC--ATGGGCTGCAGGCTGCTCT (SEQ ID NO: 758) BamHI site Kozak TCR alpha sequence TCR beta 3' (antisense): GTCGAC---TCAGAAATCCTTTCTCTTGAC (SEQ ID NO: 759) SalI site TCR beta constant sequence. Standard 35 cycle RT-PCR reactions were established using cDNA synthesized from the CTL clone and the above primers, employing the proofreading thermostable polymerase PWO (Roche, Nutley, NJ).

The resultant specific bands (approx. 850 bp for alpha and approx. 950 for beta) were ligated into the PCR blunt vector (Invitrogen) and transformed into *E. coli*. *E .coli* transformed with plasmids containing full-length alpha and beta chains were identified, and large scale preparations of the corresponding plasmids were generated. Plasmids containing full-length TCR alpha and beta chains were submitted

for sequencing. The sequencing reactions demonstrated the cloning of full-length TCR alpha and beta chains with the determined cDNA sequences for the Vb and Va chains being shown in SEQ ID NO: 760 and 761, respectively. The corresponding amino acid sequences are shown in SEQ ID NO: 762 and 763, respectively. The Va sequence was shown by nucleotide sequence alignment to be 99% identical (347/348) to Va6.2, and the Vb to be 99% identical to Vb7 (336/338).

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

What is Claimed:

1. An isolated polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(b) complements of the sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(d) sequences that hybridize to a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788 under moderately stringent conditions;

(e) sequences having at least 75% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-

375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(f) sequences having at least 90% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788; and

(g) degenerate variants of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

2. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

(b) sequences having at least 70% identity to a sequence of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

(c) sequences having at least 90% identity to a sequence of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-

629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

(d) sequences encoded by a polynucleotide of claim 1;

(e) sequences having at least 70% identity to a sequence encoded by a polynucleotide of claim 1; and

(f) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 1.

3. An expression vector comprising a polynucleotide of claim 1 operably linked to an expression control sequence.

4. A host cell transformed or transfected with an expression vector according to claim 3.

5. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 2.

6. A method for detecting the presence of a cancer in a patient, comprising the steps of:

(a) obtaining a biological sample from the patient;

(b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 2;

(c) detecting in the sample an amount of polypeptide that binds to the binding agent; and

(d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

7. A fusion protein comprising at least one polypeptide according to claim 2.

8. The fusion protein of claim 7, wherein the fusion protein comprises a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 682, 692, 695, 699, 703 and 709; and

(b) sequences encoded by SEQ ID NO: 679, 691, 696, 700, 704 and 708.

9. An oligonucleotide that hybridizes to a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 or 786-788 under moderately stringent conditions.

10. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides according to claim 2;

(b) polynucleotides according to claim 1; and

(c) antigen-presenting cells that express a polypeptide according to claim 1,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

11. An isolated T cell population, comprising T cells prepared according to the method of claim 10.

12. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:

(a) polypeptides according to claim 2;

(b) polynucleotides according to claim 1;

(c) antibodies according to claim 5;

(d) fusion proteins according to claim 7;

(e) T cell populations according to claim 11; and

(f) antigen presenting cells that express a polypeptide according to claim 2.

13. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 12.

14. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 12.

15. A method for determining the presence of a cancer in a patient, comprising the steps of:

(a) obtaining a biological sample from the patient;

(b) contacting the biological sample with an oligonucleotide according to claim 9;

(c) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

(d) compare the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.

16. A diagnostic kit comprising at least one oligonucleotide according to claim 9.

17. A diagnostic kit comprising at least one antibody according to claim 5 and a detection reagent, wherein the detection reagent comprises a reporter group.

18. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4+ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of: (i) polypeptides according to claim 2; (ii) polynucleotides according to claim 1; and (iii) antigen presenting cells that express a polypeptide of claim 2, such that T cell proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells,

thereby inhibiting the development of a cancer in the patient.

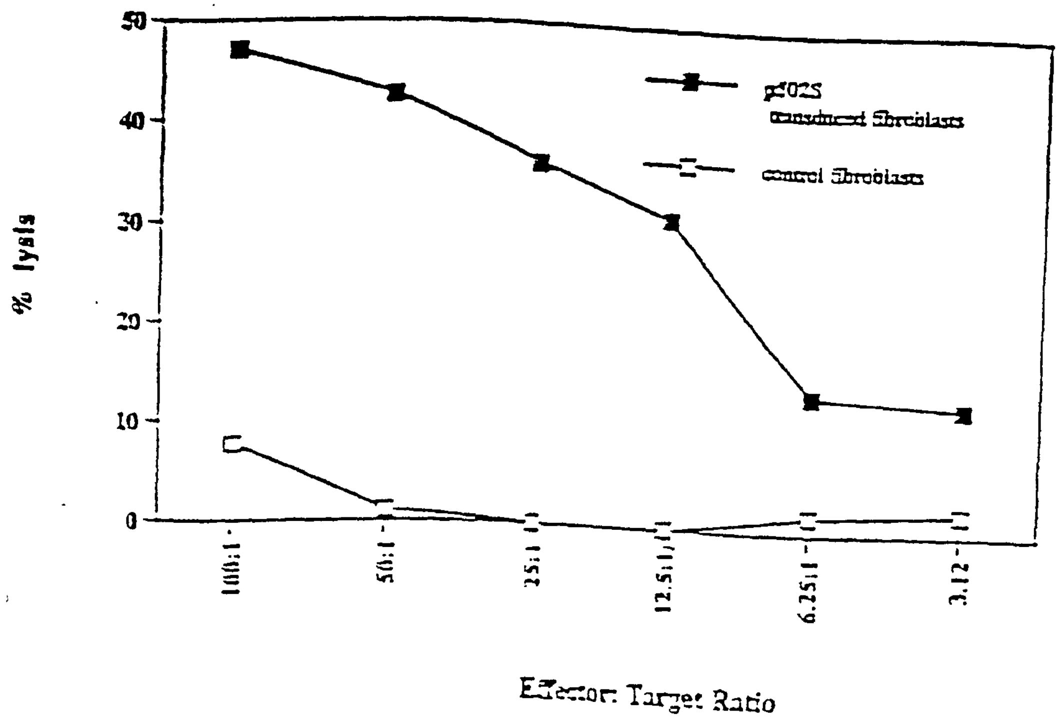

50
40
30
20
10
0
% lysis
100:1
50:1
25:1
12.5:1
6.25:1
3.12
control fibroblasts
Effector: Target Ratio

Fig. 1

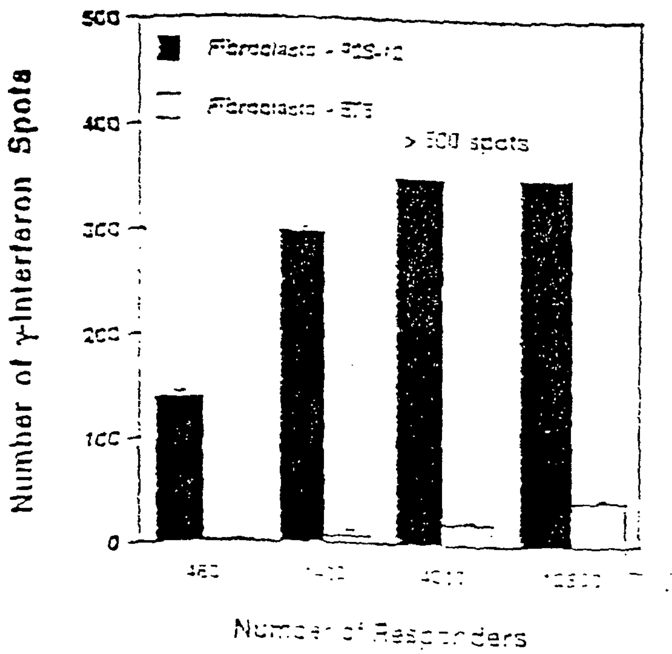


Fig. 2A

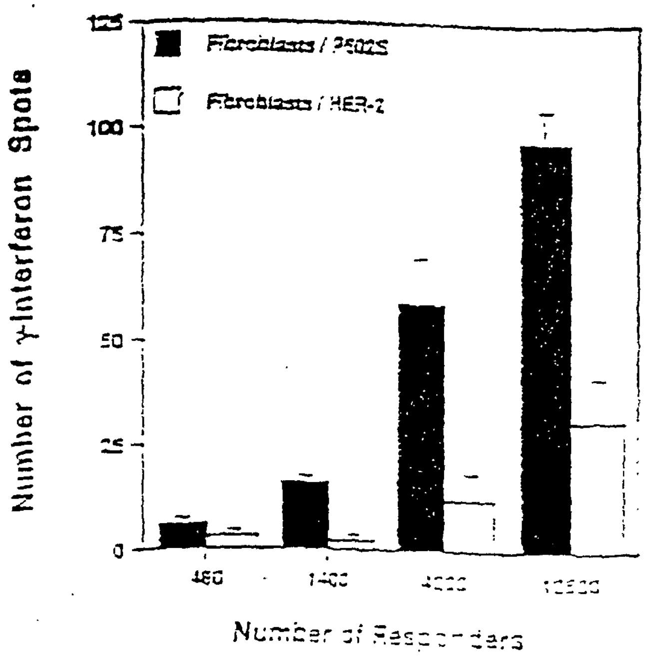

Fibroblasts / P502S
Fibroblasts / HER-2
Number of γ-Interferon Spots
Number of Responders
125
100
75
50
25
0

Fig. 2B

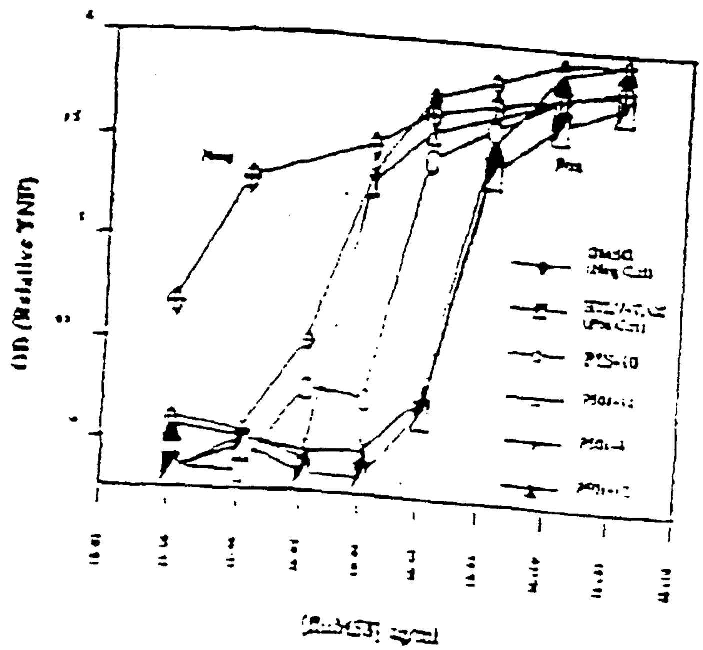


Fig. 3

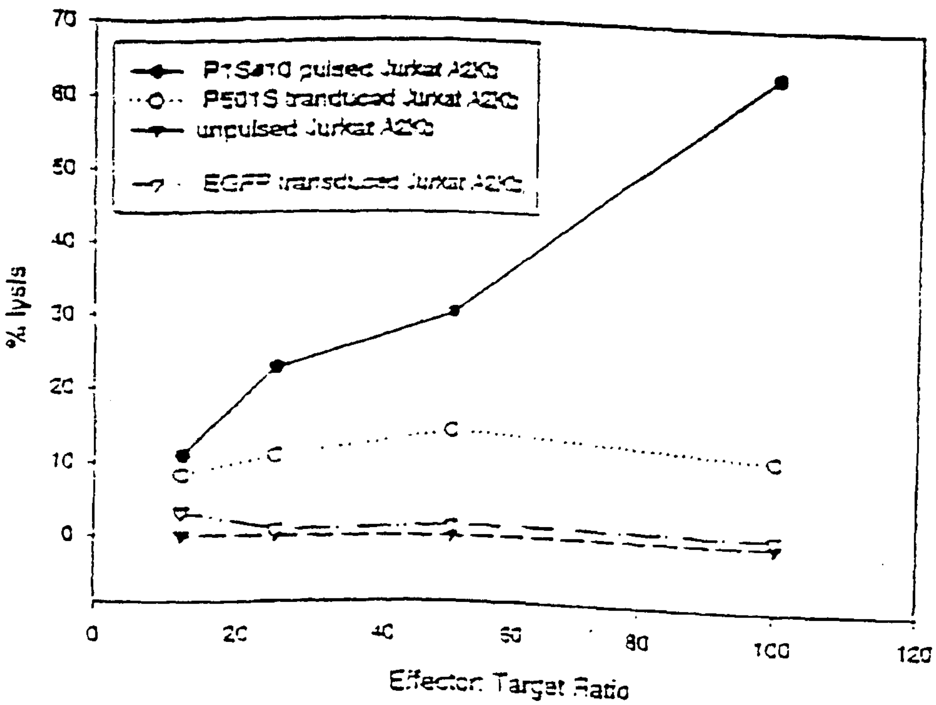

P501S pulsed Jurkat A2Kb
P501S transduced Jurkat A2Kb
unpulsed Jurkat A2Kb
EGFP transduced Jurkat A2Kb
% lysis
70
60
50
40
30
20
10
0
0
20
40
60
80
100
120
Effector: Target Ratio

Fig. 4.

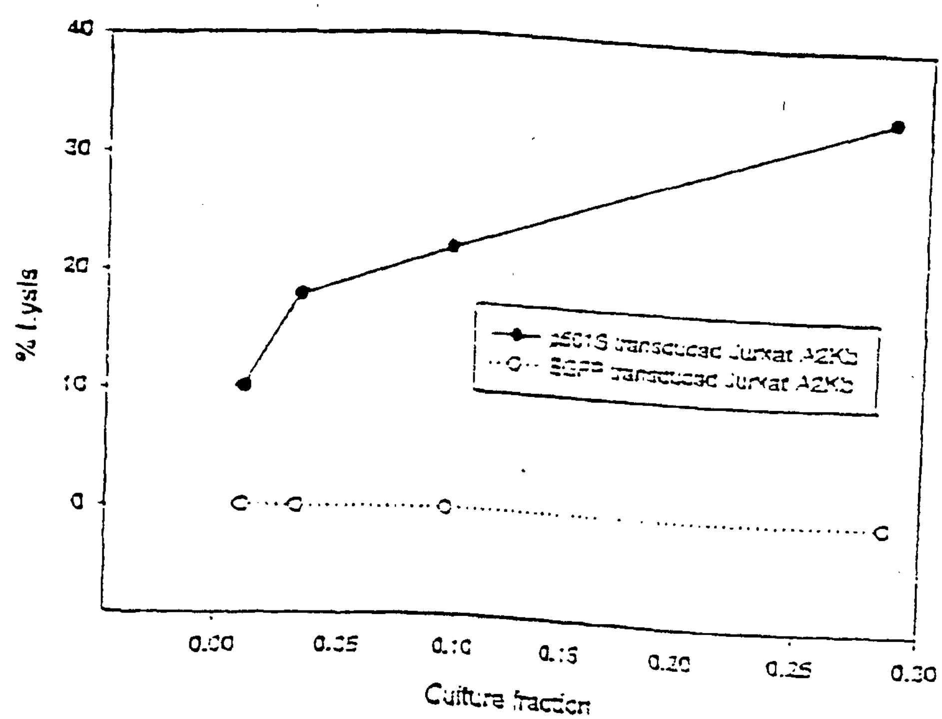

40
30
20
10
0
% Lysis
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Culture fraction

Fig. 5

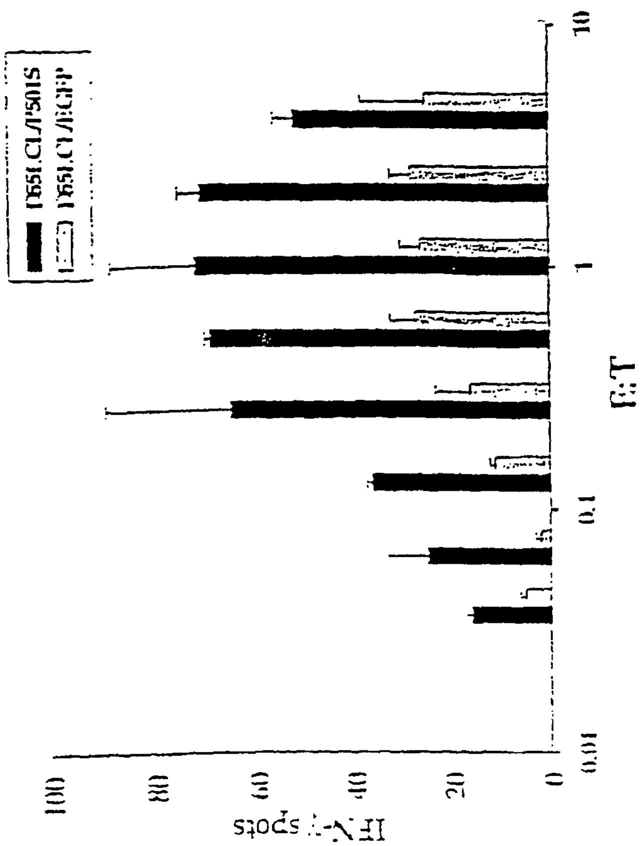

D551.C1/P501S
D551.C1/EGFP
IFN-γ spots
E:T
100
80
60
40
20
0
0.01
0.1
1
10

Fig. 6B

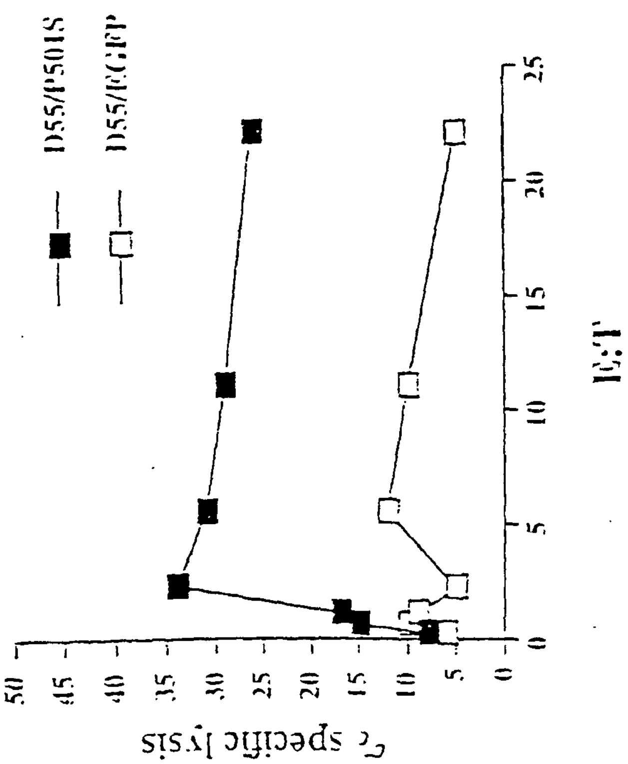
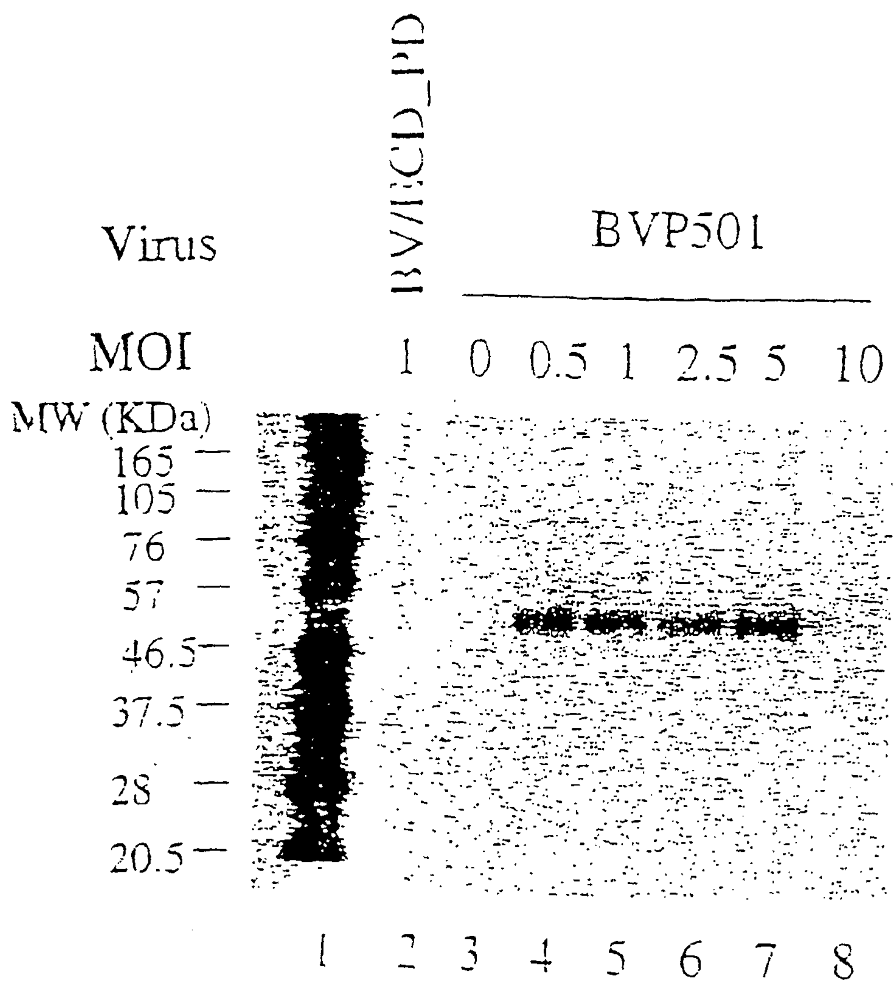

D55/P501S
D55/EGFP
% specific lysis
E:T
50
45
40
35
30
25
20
15
10
5
0
5
10
15
20
25

Fig. 6A

Expression of P501S
by the Baculovirus Expression System



0.6 million high 5 cells in 6-well plate were infected with an unrelated control virus BV/ECD_PD (lane 2), without virus (lane 3), or with recombinant baculovirus for P501 at different MOIs (lane 4 – 8). Cell lysates were run on SDS-PAGE under the reducing conditions and analyzed by Western blot with a monoclonal antibody against P501S (P501S-10E3-G4D3). Lane 1 is the biotinylated protein molecular weight marker ([illegible]).

Fig. 7

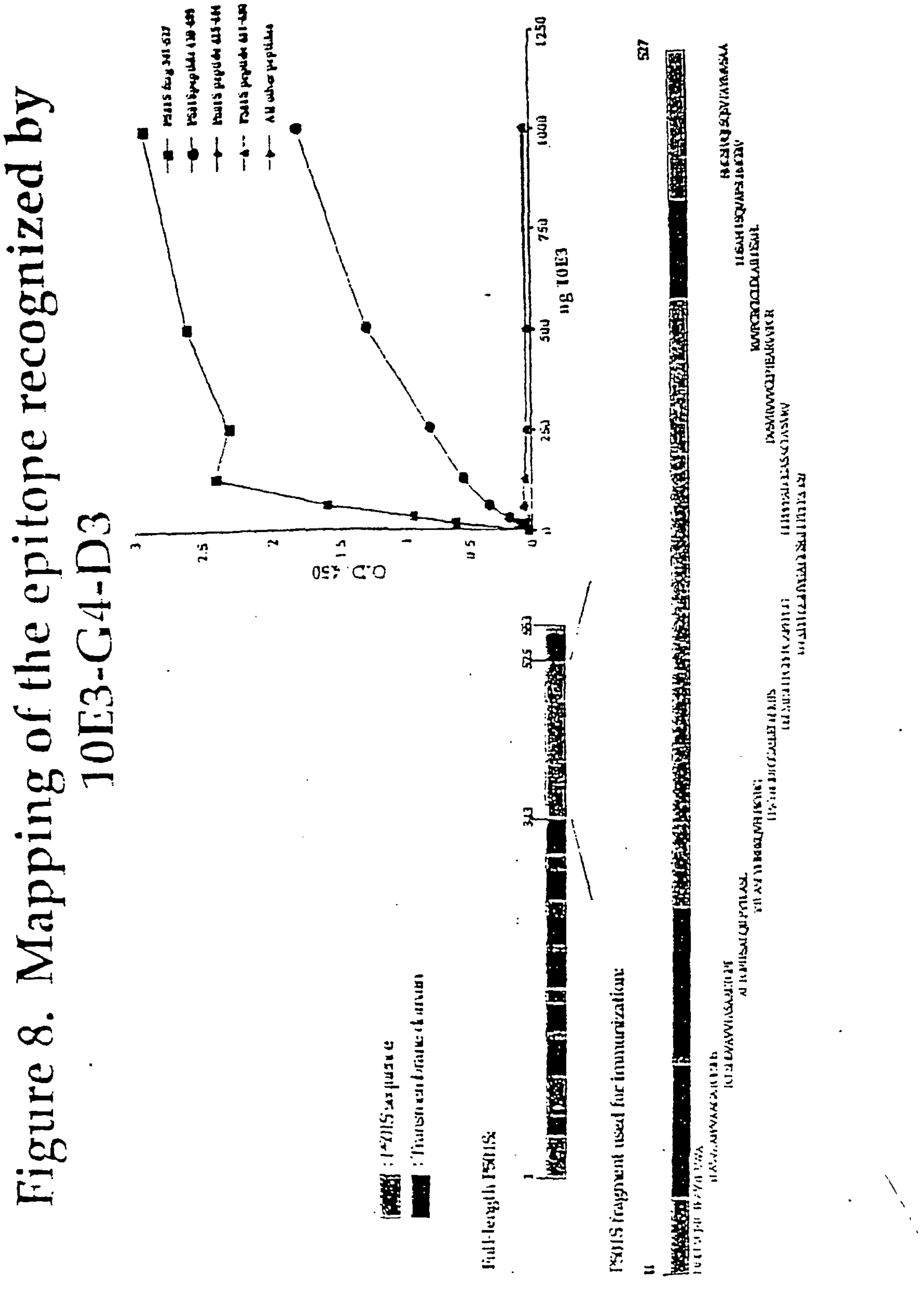


Figure 8. Mapping of the epitope recognized by 10E3-G4-D3
O.D. 450
ng 10E3
Full-length P501S
P501S fragment used for immunization
: Transmembrane domain
0
250
500
750
1000
1250
0.5
1
1.5
2
2.5
3
1
343
525
553
527

Fig. 8

Figure 1. Schematic of P501S with predicted transmembrane, cytoplasmic, and extracellular regions

MVQRLWVSRLLRHRK AQLLLVNLLTFGLEVCLAAGIT **YVPPLLLEVGVEEKFM** TMVLGIGPVLGLVCVPLLGSAS

DHWRGRYGRRRP FIWALSLGILLSLFLIPRAGWL AGLLCPDPRPLE LALLILGVGLLDFCGQVCFTPL

EALLSDLFRDPDHCRQ AYSVYAFMISLGGCLGYLLPAI **DWDTSALAPYLGTQEE**

CLFGLLTLIFLTCVAATLLV *AEEAALGPTEPAEGLSAPSLSPHCCPCRARLAFRNLGALLPRL*

HQLCCRMPRTLRR LFVAELCSWMALMTFTLFYTDF **VGEGLYQGVPRAEPGTEARRHYDEGVR**

MGSLGLFLQCAISLVFSLVM *DRLVQRFGTRAVYLAS* VAAFPVAAGATCLSHSVAVVTA **SAA**

LTGFTFSALQILPYTLASLY *HREKQVFLPKYRGDTGGASSEDSLMTSFLPGPKPGAPFPNGHVGAGGSGL*

LPPPPALCGASACDVSVRVVVGEPTEARVVPGRG ICLDLAILDSALLLSQVAPSLF **MGSIVQLSQS**

VTAYMVSAAGLGLVAIYFAT *QVVFDKSDLAKYSA*

Underlined sequence: Predicted transmembrane domain; **Bold sequence**: Predicted extracellular domain; *Italic sequence*: Predicted intracellular domain. Sequence in bold/underlined: used to generate polyclonal rabbit serum

Localization of domains predicted using HMMTOP (G.E. Tusnady and I. Simon (1998) Principles Governing Amino Acid Composition of Integral Membrane Proteins: Applications to topology Prediction.J.Mol Biol. 283, 489-506.

Fig. 9

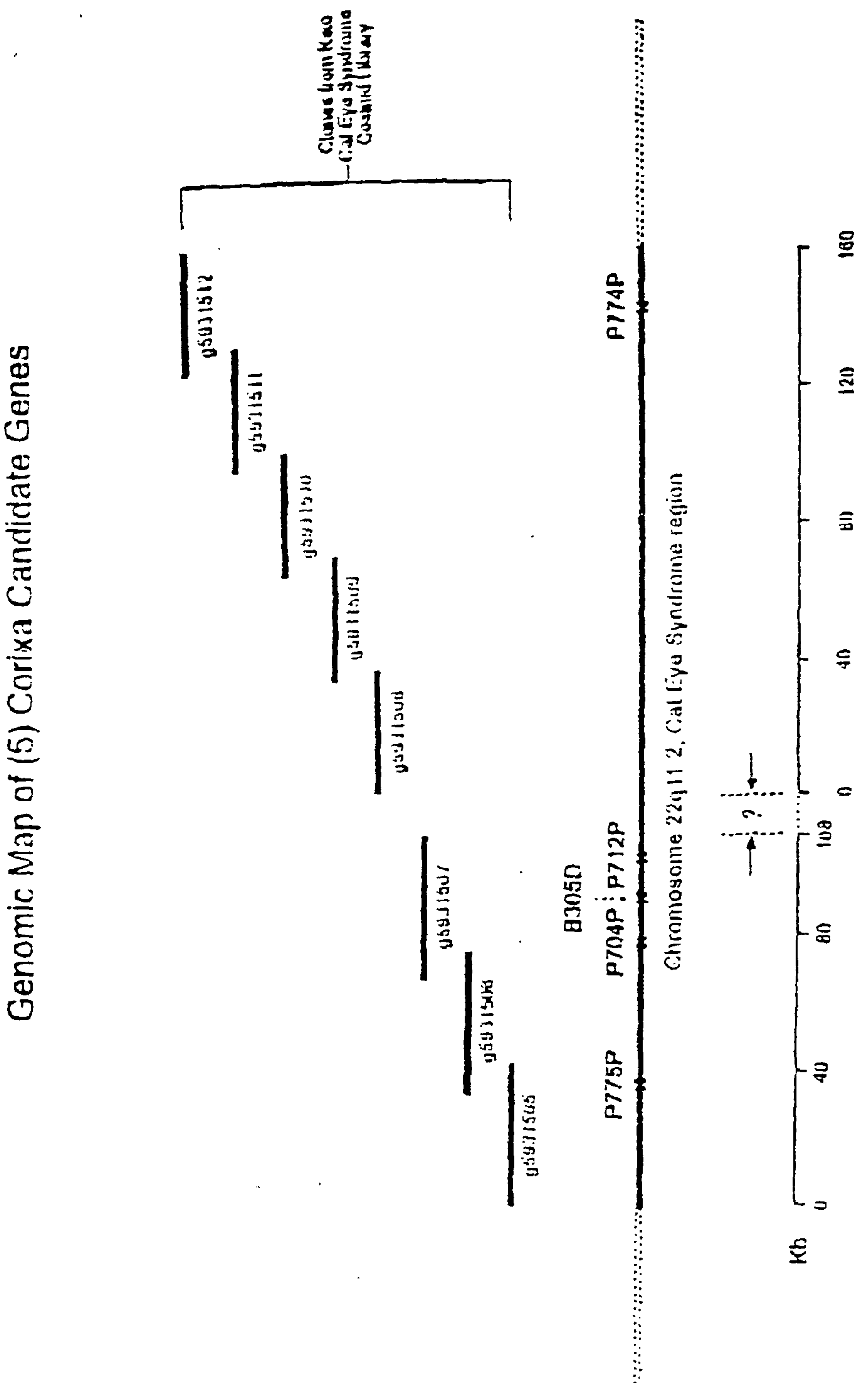

Genomic Map of (5) Corixa Candidate Genes
Clones from Keio Cat Eye Syndrome Cosmid Library
P775P
P704P
P712P
B305D
P774P
Chromosome 22q11.2, Cat Eye Syndrome region
?
Kb
0
40
80
0
40
80
120
160

Fig. 10

FIGURE 4. Elisa assay of rabbit polyclonal antibody specificity

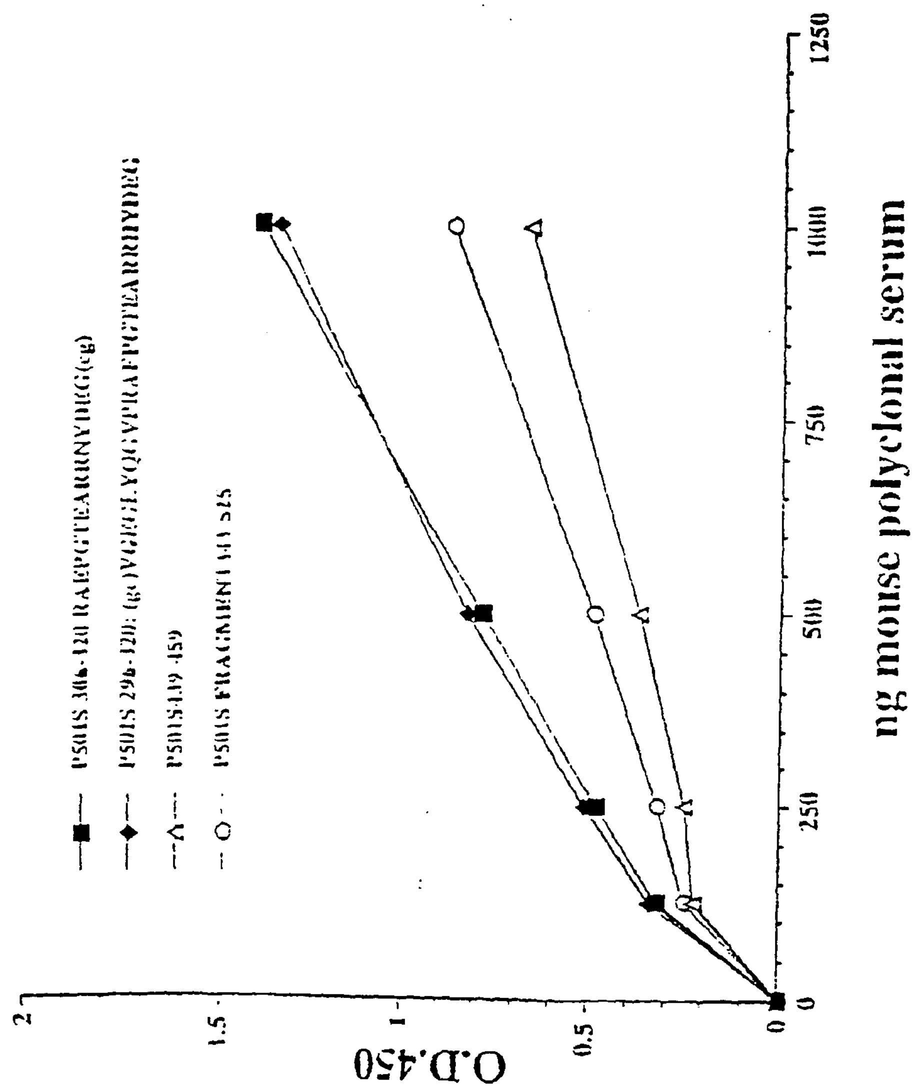


Fig. 11

SEQUENCE LISTING

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Smithkline Beechan Biologicals S.A.
Xu, Jiangchun
Dillon, Davin C.
Mitcham, Jennifer L.
Harlocker, Susan L.
Jiang, Yuqui
Reed, Steven G.
Kalos, Michael D.
Fanger, Gary R.
Retter, Marc W.
Stolk, John A.
Day, Craig H.
Skeiky, Yasir A.W.
Wang, Aijun
Meagher, Medeleine Joy
Vanderbrugge, Didier
Dewerchin, Marianne
Dehottay, Ph.
de Rop, Philippe

<120> COMPOSITIONS AND METHODS FOR THE THERAPY AND
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atcaaatctg agggttgtct ggaggacttc aatacacctc cccccatagt gaatcagctt     120
ccaggggtc cagtccctct ccttacttca tccccatccc atgccaaagg aagaccctcc      180
ctccttggct cacagccttc tctaggcttc ccagtgcctc caggacagag tgggttatgt     240
tttcagctcc atccttgctg tgagtgtctg gtgcgttgtg cctccagctt ctgctcagtg     300
cttcatggac agtgtccagc acatgtcact ctccactctc tcagtgtgga tccactagtt     360
ctagagcggc cgccaccgcg gtggagctcc agcttttgtt ccctttagtg agggttaatt     420
gcgcgcttgg cgtaatcatg gtcataactg tttcctgtgt gaaattgtta tccgctcaca     480
attccacaca acatacgagc cggaagcata aagtgtaaag cctggggtgc ctaatgagtg     540
anctaactca cattaattgc gttgcgctca ctgnccgctt tccagtcngg aaaactgtcg     600
tgccagctgc attaatgaat cggccaacgc ncggggaaaa gcggtttgcg ttttgggggc     660
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tcttccgctt ctcgctcact nantcctgcg ctcggtcntt cggctgcggg gaacggtatc 720
actcctcaaa ggnggtatta cggttatccn naaatcnggg gatacccngg aaaaaanttt 780
aacaaaaggg cancaaaggg cngaaacgta aaaa 814

<210> 2
<211> 816
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(816)
<223> n = A,T,C or G

<400> 2
acagaaatgt tggatggtgg agcacctttc tatacgactt acaggacagc agatggggaa 60
ttcatggctg ttggagcaat agaaccccag ttctacgagc tgctgatcaa aggacttgga 120
ctaaagtctg atgaacttcc caatcagatg agcatggatg attggccaga aatgaagaag 180
aagtttgcag atgtatttgc aaagaagacg aaggcagagt ggtgtcaaat ctttgacggc 240
acagatgcct gtgtgactcc ggttctgact tttgaggagg ttgttcatca tgatcacaac 300
aaggaacggg gctcgtttat caccagtgag gagcaggacg tgagccccccg ccctgcacct 360
ctgctgttaa acaccccagc catcccttct ttcaaaaggg atccactagt tctagaagcg 420
gccgccaccg cggtggagct ccagcttttg ttccctttag tgagggttaa ttgcgcgctt 480
ggcgtaatca tggtcatagc tgtttcctgt gtgaaattgt tatccgctca caattccccc 540
aacatacgag ccggaacata aagtgttaag cctggggtgc ctaatgantg agctaactcn 600
cattaattgc gttgcgctca ctgcccgctt tccagtcggg aaaactgtcg tgccactgcn 660
ttantgaatc ngccaccccc cgggaaaagg cggttgcntt ttgggcctct tccgctttcc 720
tcgctcattg atcctngcnc ccggtcttcg gctgcggnga acggttcact cctcaaaggc 780
ggtntnccgg ttatccccaa acnggggata cccnga 816

<210> 3
<211> 773
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(773)
<223> n = A,T,C or G

<400> 3
cttttgaaag aagggatggc tggggtgttt aacagcagag gtgcagggcg ggggctcacg 60
tcctgctcct cactggtgat aaacgagccc cgttccttgt tgtgatcatg atgaacaacc 120
tcctcaaaag tcagaaccgg agtcacacag gcatctgtgc cgtcaaagat ttgacaccac 180
tctgccttcg tcttctttgc aaatacatct gcaaacttct tcttcatttc tggccaatca 240
tccatgctca tctgattggg aagttcatca gactttagtc canntccttt gatcagcagc 300
tcgtagaact ggggttctat tgctccaaca gccatgaatt ccccatctgc tgtcctgtaa 360
gtcgtataga aaggtgctcc accatccaac atgttctgtc ctcgaggggg ggcccggtac 420
ccaattcgcc ctatantgag tcgtattacg cgcgctcact ggccgtcgtt ttacaacgtc 480
gtgactggga aaaccctggg cgttaccaac ttaatcgcct tgcagcacat ccccctttcg 540
ccagctgggc gtaatancga aaggcccgc accgatcgcc cttccaacag ttgcgcacct 600
gaatgggnaa atggacccc cctgttaccg cgcattnaac ccccgcnggg tttngttgtt 660
acccccacnt nnaccgctta cactttgcca gcgccttanc gcccgctccc tttcnccttt 720
cttcccttcc tttcncnccn ctttcccccg gggtttcccc cntcaaaccc cna 773

<210> 4
<211> 828
<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(828)
<223> n = A,T,C or G

<400> 4
cctcctgagt cctactgacc tgtgctttct ggtgtggagt ccagggctgc taggaaaagg 60
aatgggcaga cacaggtgta tgccaatgtt tctgaaatgg gtataatttc gtcctctcct 120
tcggaacact ggctgtctct gaagacttct cgctcagttt cagtgaggac acacacaaag 180
acgtgggtga ccatgttgtt tgtggggtgc agagatggga ggggtggggc ccaccctgga 240
agagtggaca gtgacacaag gtggacactc tctacagatc actgaggata agctggagcc 300
acaatgcatg aggcacacac acagcaagga tgacnctgta aacatagccc acgctgtcct 360
gngggcactg ggaagcctan atnaggccgt gagcanaaag aaggggagga tccactagtt 420
ctanagcggc cgccaccgcg gtgganctcc anctttttgtt cccctttagtg agggttaatt 480
gcgcgcttgg cntaatcatg gtcatanctn tttcctgtgt gaaattgtta tccgctcaca 540
attccacaca acatacganc cggaaacata aantgtaaac ctggggtgcc taatgantga 600
ctaactcaca ttaattgcgt tgcgctcact gcccgctttc caatcnggaa acctgtcttg 660
ccncttgcat tnatgaatcn gccaaccccc ggggaaaagc gtttgcgttt tgggcgctct 720
tccgcttcct cnctcantta ntccctncnc tcggtcattc cggctgcngc aaaccggttc 780
accncctcca aaggggtat tccggtttcc ccnaatccgg gganancc 828

<210> 5
<211> 834
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(834)
<223> n = A,T,C or G

<400> 5
tttttttttt tttttactga tagatggaat ttattaagct tttcacatgt gatagcacat 60
agttttaatt gcatccaaag tactaacaaa aactctagca atcaagaatg gcagcatgtt 120
attttataac aatcaacacc tgtggctttt aaaatttggt tttcataaga taatttatac 180
tgaagtaaat ctagccatgc ttttaaaaaa tgctttaggt cactccaagc ttggcagtta 240
acatttggca taaacaataa taaaacaatc acaatttaat aaataacaaa tacaacattg 300
taggccataa tcatatacag tataaggaaa aggtggtagt gttgagtaag cagttattag 360
aatagaatac cttggcctct atgcaaatat gtctagacac tttgattcac tcagccctga 420
cattcagttt tcaaagtagg agacaggttc tacagtatca ttttacagtt tccaacacat 480
tgaaaacaag tagaaaatga tgagttgatt tttattaatg cattacatcc tcaagagtta 540
tcaccaaccc ctcagttata aaaaattttc aagttatatt agtcatataa cttggtgtgc 600
ttattttaaa ttagtgctaa atggattaag tgaagacaac aatggtcccc taatgtgatt 660
gatattggtc atttttacca gcttctaaat ctnaactttc aggcttttga actggaacat 720
tgnatnacag tgttccanag ttncaaccta ctggaacatt acagtgtgct tgattcaaaa 780
tgttattttg ttaaaaatta aattttaacc tggtggaaaa ataatttgaa atna 834

<210> 6
<211> 818
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(818)
<223> n = A,T,C or G

<400> 6
tttttttttt tttttttttt aagaccctca tcaatagatg gagacataca gaaatagtca 60
aaccacatct acaaaatgcc agtatcaggc ggcggcttcg aagccaaagt gatgtttgga 120
tgtaaagtga aatattagtt ggcggatgaa gcagatagtg aggaaagttg agccaataat 180
gacgtgaagt ccgtggaagc ctgtggctac aaaaaatgtt gagccgtaga tgccgtcgga 240
aatggtgaag ggagactcga agtactctga ggcttgtagg agggtaaaat agagacccag 300
taaaattgta ataagcagtg cttgaattat ttggtttcgg ttgttttcta ttagactatg 360
gtgagctcag gtgattgata ctcctgatgc gagtaatacg gatgtgttta ggagtgggac 420
ttctagggga tttagcgggg tgatgcctgt tgggggccag tgccctccta gttgggggt 480
aggggctagg ctggagtggt aaaaggctca gaaaaatcct gcgaagaaaa aaacttctga 540
ggtaataaat aggattatcc cgtatcgaag gcctttttgg acaggtggtg tgtggtggcc 600
ttggtatgtg ctttctcgtg ttacatcgcg ccatcattgg tatatggtta gtgtgttggg 660
ttantanggc ctantatgaa gaacttttgg antggaatta aatcaatngc ttggccggaa 720
gtcattanga nggctnaaaa ggccctgtta ngggtctggg ctnggtttta cccnacccat 780
ggaatncncc ccccggacna ntgnatccct attcttaa 818

<210> 7
<211> 817
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(817)
<223> n = A,T,C or G

<400> 7
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ggtttgctcc acagatttca gagcattgac cgtagtatac cccggtcgt gtagcggtga 180
aagtggtttg gtttagacgt ccgggaattg catctgtttt taagcctaat gtggggacag 240
ctcatgagtg caagacgtct tgtgatgtaa ttattatacn aatgggggct tcaatcggga 300
gtactactcg attgtcaacg tcaaggagtc gcaggtcgcc tggttctagg aataatgggg 360
gaagtatgta ggaattgaag attaatccgc cgtagtcggt gttctcctag gttcaatacc 420
attggtggcc aattgatttg atggtaaggg gagggatcgt tgaactcgtc tgttatgtaa 480
aggatncctt ngggatggga aggcnatnaa ggactangga tnaatggcgg gcangatatt 540
tcaaacngtc tctanttcct gaaacgtctg aaatgttaat aanaattaan tttngttatt 600
gaatnttnng gaaaagggct tacaggacta gaaaccaaat angaaaanta atnntaangg 660
cnttatcntn aaaggtnata accnctccta tnatcccacc caatngnatt ccccacncnn 720
acnattggat nccccanttc canaaanggc cnccccccgg tgnannccnc cttttgttcc 780
cttnantgan ggttattcnc ccctngcntt atcancc 817

<210> 8
<211> 799
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(799)
<223> n = A,T,C or G

<400> 8
catttccggg tttactttct aaggaaagcc gagcggaagc tgctaacgtg ggaatcggtg 60
cataaggaga actttctgct ggcacgcgct agggacaagc gggagagcga ctccgagcgt 120
ctgaagcgca cgtcccagaa ggtggacttg gcactgaaac agctgggaca catccgcgag 180
tacgaacagc gcctgaaagt gctggagcgg gaggtccagc agtgtagccg cgtcctgggg 240

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tgggtggccg angcctganc cgctctgcct tgctgccccc angtgggccg ccaccccctg 300
acctgcctgg gtccaaacac tgagccctgc tggcggactt caagganaac ccccacangg 360
ggattttgct cctanantaa ggctcatctg ggcctcggcc cccccacctg gttggccttg 420
tctttgangt gagccccatg tccatctggg ccactgtcng gaccaccttt ngggagtgtt 480
ctccttacaa ccacannatg cccggctcct cccggaaacc antcccancc tgngaaggat 540
caagncctgn atccactnnt nctanaaccg gccnccnccg cngtggaacc cnccttntgt 600
tccttttcnt tnagggttaa tnncgccttg gccttnccan ngtcctncnc nttttccnnt 660
gttnaaattg ttangcnccc nccnntcccn cnncnncnan cccgacccnn annttnnann 720
ncctgggggt nccnncngat tgacccnncc nccctntant tgcnttnggg nncnntgccc 780
ctttccctct ngggannccg 799
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<210> 9
<211> 801
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(801)
<223> n = A,T,C or G

<400> 9

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taangatgac actcccaaag gtggtcctga cagtggccca gatggacatg gggctcacct 120
caaggacaag gccaccaggt gcgggggccg aagcccacat gatccttact ctatgagcaa 180
aatcccctgt gggggcttct ccttgaagtc cgccancagg gctcagtctt tggacccang 240
caggtcatgg ggttgtngnc caactggggg ccncaacgca aaanggcnca gggcctcngn 300
cacccatccc angacgcggc tacactnctg gacctcccnc tccaccactt tcatgcgctg 360
ttcntacccg cgnatntgtc ccanctgttt cngtgccnac tccancttct nggacgtgcg 420
ctacatacgc ccggantcnc nctcccgctt tgtccctatc cacgtnccan caacaaattt 480
cnccntantg caccnattcc cacntttnnc agntttccnc nncgngcttc cttntaaaag 540
ggttganccc cggaaaatnc cccaaagggg gggggccngg tacccaactn cccccntata 600
gctgaantcc ccatnaccnn gnctcnatgg ancentcent tttaannacn ttctnaactt 660
gggaanancc ctcgnccntn ccccenttaa tcccnccttg cnangnncnt cccccnntcc 720
ncccnnntng gcntntnann cnaaaaaggc ccnnnancaa tctcctnncn cctcanttcg 780
ccanccctcg aaatcggccn c 801
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<210> 10
<211> 789
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(789)
<223> n = A,T,C or G

<400> 10

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acagtgtggc cgtggtgaca gcttcagccg ccctcaccgg gttcaccttc tcagccctgc 120
agatcctgcc ctacacactg gcctccctct accaccggga gaagcaggtg ttcctgccca 180
aataccgagg ggacactgga ggtgctagca gtgaggacag cctgatgacc agcttcctgc 240
caggccctaa gcctggagct cccttcccta atggacacgt gggtgctgga ggcagtggcc 300
tgctcccacc tccacccgcg ctctgcgggg cctctgcctg tgatgtctcc gtacgtgtgg 360
tggtgggtga gcccaccgan gccagggtgg ttccgggccg gggcatctgc ctggacctcg 420
ccatcctgga tagtgcttcc tgctgtccca ngtggcccca tccctgttta tgggctccat 480
tgtccagctc agccagtctg tcactgccta tatggtgtct gccgcaggcc tgggtctggt 540
cccatttact ttgctacaca ggtantattt gacaagaacg anttggccaa atactcagcg 600
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ttaaaaaatt ccagcaacat tgggggtgga aggcctgcct cactgggtcc aactccccgc 660
tcctgttaac cccatggggc tgccggcttg gccgccaatt tctgttgctg ccaaantnat 720
gtggctctct gctgccacct gttgctggct gaagtgcnta cngcncanct ngggggtng 780
ggngttccc 789

<210> 11
<211> 772
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(772)
<223> n = A,T,C or G

<400> 11
cccaccctac ccaaatatta gacaccaaca cagaaaagct agcaatggat tcccttctac 60
tttgttaaat aaataagtta aatatttaaa tgcctgtgtc tctgtgatgg caacagaagg 120
accaacaggc cacatcctga taaaaggtaa gaggggggtg gatcagcaaa aagacagtgc 180
tgtgggctga ggggacctgg ttcttgtgtg ttgcccctca ggactcttcc cctacaaata 240
actttcatat gttcaaatcc catggaggag tgtttcatcc tagaaactcc catgcaagag 300
ctacattaaa cgaagctgca ggttaagggg cttanagatg ggaaaccagg tgactgagtt 360
tattcagctc ccaaaaaccc ttctctaggt gtgtctcaac taggaggcta gctgttaacc 420
ctgagcctgg gtaatccacc tgcagagtcc ccgcattcca gtgcatggaa cccttctggc 480
ctccctgtat aagtccagac tgaaaccccc ttggaaggnc tccagtcagg cagccctana 540
aactggggaa aaaagaaaag gacgccccan cccccagctg tgcanctacg cacctcaaca 600
gcacagggtg gcagcaaaaa aaccacttta ctttggcaca aacaaaaact ngggggggca 660
accccggcac cccnangggg gttaacagga ancngggnaa cntggaaccc aattnaggca 720
ggcccnccac cccnaatntt gctgggaaat ttttcctccc ctaaattntt tc 772

<210> 12
<211> 751
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(751)
<223> n = A,T,C or G

<400> 12
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agctgattga agcaaccctc tactttttgg tcgtgagcct tttgcttggt gcaggtttca 120
ttggctgtgt tggtgacgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg 180
aagtanggtg agtcctcaaa atccgtatag ttggtgaagc cacagcactt gagccctttc 240
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ggcactacca gcaacgtcag ggaagtgctc agccattgtg gtgtacacca aggcgaccac 360
agcagctgcn acctcagcaa tgaagatgan gaggangatg aagaagaacg tcncgagggc 420
acacttgctc tcagtcttan caccatanca gcccntgaaa accaananca aagaccacna 480
cnccggctgc gatgaagaaa tnaccccncg ttgacaaact tgcatggcac tggganccac 540
agtggcccna aaaatcttca aaaaggatgc cccatcnatt gaccccccaa atgcccactg 600
ccaacagggg ctgccccacn cncnnaacga tganccnatt gnacaagatc tncntggtct 660
tnatnaacnt gaaccctgcn tngtggctcc tgttcaggnc cnnggcctga cttctnaann 720
aangaactcn gaagncccca cngganannc g 751

<210> 13
<211> 729
<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(729)
<223> n = A,T,C or G

<400> 13
gagccaggcg tccctctgcc tgcccactca gtggcaacac ccgggagctg ttttgtcctt 60
tgtggancct cagcagtncc ctctttcaga actcantgcc aagancccctg aacaggagcc 120
accatgcagt gcttcagctt cattaagacc atgatgatcc tcttcaattt gctcatcttt 180
ctgtgtggtg cagccctgtt ggcagtgggc atctgggtgt caatcgatgg ggcatccttt 240
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actgagagca agtgtgccct cgtgacgttc ttcttcatcc tcctcctcat cttcattgct 420
gaggttgcaa tgctgtggtc gccttggtgt acaccacaat ggctgagcac ttcctgacgt 480
tgctggtaat gcctgccatc aanaaaagat tatgggttcc caggaanact tcactcaagt 540
gttggaacac caccatgaaa gggctcaagt gctgtggctt cnnccaacta tacggatttt 600
gaagantcac ctacttcaaa gaaaanagtg cctttccccc atttctgttg caattgacaa 660
acgtccccaa cacagccaat tgaaaacctg cacccaaccc aaangggtcc ccaaccanaa 720
attnaaggg 729

<210> 14
<211> 816
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(816)
<223> n = A,T,C or G

<400> 14
tgctcttcct caaagttgtt cttgttgcca taacaaccac cataggtaaa gcgggcgcag 60
tgttcgctga aggggttgta gtaccagcgc gggatgctct ccttgcagag tcctgtgtct 120
ggcaggtcca cgcagtgccc tttgtcactg gggaaatgga tgcgctggag ctcgtcaaag 180
ccactcgtgt atttttcaca ggcagcctcg tccgacgcgt cggggcagtt gggggtgtct 240
tcacactcca ggaaactgtc natgcagcag ccattgctgc agcggaactg ggtgggctga 300
cangtgccag agcacactgg atggcgcctt tccatgnnan gggccctgng ggaaagtccc 360
tganccccan anctgcctct caaangcccc accttgcaca ccccgacagg ctagaatgga 420
atcttcttcc cgaaaggtag ttnttcttgt tgcccaancc anccccntaa acaaactctt 480
gcanatctgc tccgnggggg tcntantacc ancgtgggaa aagaacccca ggcngcgaac 540
caancttgtt tggatncgaa gcnataatct nctnttctgc ttggtggaca gcaccantna 600
ctgtnnanct ttagnccntg gtcctcntgg gttgnncttg aacctaatcn ccnntcaact 660
gggacaaggt aantngccnt cctttnaatt cccnancntn ccccctggtt tggggttttn 720
cncnctccta ccccagaaan nccgtgttcc cccccaacta ggggccnaaa ccnnttnttc 780
cacaaccctn ccccacccac gggttcngnt ggttng 816

<210> 15
<211> 783
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(783)
<223> n = A,T,C or G

<400> 15
ccaaggcctg ggcaggcata nacttgaagg tacaacccca ggaacccctg gtgctgaagg 60
atgtggaaaa cacagattgg cgcctactgc ggggtgacac ggatgtcagg gtagagagga 120
aagacccaaa ccaggtggaa ctgtggggac tcaaggaang cacctacctg ttccagctga 180
cagtgactag ctcagaccac ccagaggaca cggccaacgt cacagtcact gtgctgtcca 240
ccaagcagac agaagactac tgcctcgcat ccaacaangt gggtcgctgc cggggctctt 300
tcccacgctg gtactatgac cccacggagc agatctgcaa gagtttcgtt tatggaggct 360
gcttgggcaa caagaacaac taccttcggg aagaagagtg cattctancc tgtcngggtg 420
tgcaaggtgg gcctttgana ngcanctctg gggctcangc gactttcccc cagggcccct 480
ccatggaaag gcgccatcca ntgttctctg gcacctgtca gcccacccag ttccgctgca 540
ncaatggctg ctgcatcnac antttcctng aattgtgaca acacccccca ntgcccccaa 600
ccctcccaac aaagcttccc tgttnaaaaa tacnccantt ggcttttnac aaacnccccgg 660
cncctccntt ttccccnntn aacaaagggc nctngcnttt gaactgcccn aacccnggaa 720
tctnccnngg aaaaantncc ccccctggtt cctnnaancc cctccncnaa anctnccccc 780
ccc 783

<210> 16
<211> 801
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(801)
<223> n = A,T,C or G

<400> 16
gccccaattc cagctgccac accacccacg gtgactgcat tagttcggat gtcatacaaa 60
agctgattga agcaaccctc tacttttttgg tcgtgagcct tttgcttggt gcaggtttca 120
ttggctgtgt tggtgacgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg 180
aagtagggtg agtcctcaaa atccgtatag ttggtgaagc cacagcactt gagccctttc 240
atggtggtgt tccacacttg agtgaagtct tcctgggaac cataatcttt cttgatggca 300
ggcactacca gcaacgtcag gaagtgctca gccattgtgg tgtacaccaa ggcgaccaca 360
gcagctgcaa cctcagcaat gaagatgagg aggaggatga agaagaacgt cncgagggca 420
cacttgctct ccgtcttagc accatagcag cccangaaac caagagcaaa gaccacaacg 480
ccngctgcga atgaaagaaa ntacccacgt tgacaaactg catggccact ggacgacagt 540
tggcccgaan atcttcagaa aagggatgcc ccatcgattg aacacccana tgcccactgc 600
cnacagggct gcnccncncn gaaagaatga gccattgaag aaggatcntc ntggtcttaa 660
tgaactgaaa ccntgcatgg tggcccctgt tcagggctct tggcagtgaa ttctganaaa 720
aaggaacngc ntnagccccc ccaaangana aaacaccccc gggtgttgcc ctgaattggc 780
ggccaaggan ccctgccccn g 801

<210> 17
<211> 740
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(740)
<223> n = A,T,C or G

<400> 17
gtgagagcca ggcgtccctc tgcctgccca ctcagtggca acacccggga gctgttttgt 60
cctttgtgga gcctcagcag ttccctcttt cagaactcac tgccaagagc cctgaacagg 120
agccaccatg cagtgcttca gcttcattaa gaccatgatg atcctcttca atttgctcat 180
ctttctgtgt ggtgcagccc tgttggcagt gggcatctgg gtgtcaatcg atggggcatc 240
ctttctgaag atcttcgggc cactgtcgtc cagtgccatg cagtttgtca acgtgggcta 300

cttcctcatc gcagccggcg ttgtggtctt tgctcttggt ttcctgggct gctatggtgc 360
taagacggag agcaagtgtg ccctcgtgac gttcttcttc atcctcctcc tcatcttcat 420
tgctgaagtt gcagctgctg tggtcgcctt ggtgtacacc acaatggctg aaccattcct 480
gacgttgctg gtantgcctg ccatcaanaa agattatggg ttcccaggaa aaattcactc 540
aantntggaa caccnccatg aaaagggctc caatttctgn tggcttcccc aactataccg 600
gaattttgaa agantcnccc tacttccaaa aaaaaanant tgcctttncc cccnttctgt 660
tgcaatgaaa acntcccaan acngccaatn aaaacctgcc cnnncaaaaa ggntcncaaa 720
caaaaaaant nnaagggttn 740

<210> 18
<211> 802
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(802)
<223> n = A,T,C or G

<400> 18
ccgctggttg cgctggtcca gngnagccac gaagcacgtc agcatacaca gcctcaatca 60
caaggtcttc cagctgccgc acattacgca gggcaagagc ctccagcaac actgcatatg 120
ggatacactt tactttagca gccagggtga caactgagag gtgtcgaagc ttattcttct 180
gagcctctgt tagtggagga agattccggg cttcagctaa gtagtcagcg tatgtcccat 240
aagcaaacac tgtgagcagc cggaaggtag aggcaaagtc actctcagcc agctctctaa 300
cattgggcat gtccagcagt tctccaaaca cgtagacacc agnggcctcc agcacctgat 360
ggatgagtgt ggccagcgct gccccccttgg ccgacttggc taggagcaga aattgctcct 420
ggttctgccc tgtcaccttc acttccgcac tcatcactgc actgagtgtg ggggacttgg 480
gctcaggatg tccagagacg tggttccgcc ccctcnctta atgacaccgn ccanncaacc 540
gtcggctccc gccgantgng ttcgtcgtnc ctgggtcagg gtctgctggc cnctacttgc 600
aancttcgtc nggcccatgg aattcaccnc accggaactn gtangatcca ctnnttctat 660
aaccggncgc caccgcnnnt ggaactccac tcttnttncc tttacttgag ggttaaggtc 720
accсttnncg ttaccttggt ccaaaccntn ccntgtgtcg anatngtnaa tcnggnccna 780
tnccanccnc atangaagcc ng 802

<210> 19
<211> 731
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(731)
<223> n = A,T,C or G

<400> 19
cnaagcttcc aggtnacggg ccgcnaancc tgacccnagg tancanaang cagncngcgg 60
gagcccaccg tcacgnggng gngtctttat nggaggggc ggagccacat cnctggacnt 120
cntgacccca actccccncc ncncantgca gtgatgagtg cagaactgaa ggtnacgtgg 180
caggaaccaa gancaaannc tgctccnntc caagtcggcn nagggggcgg ggctggccac 240
gcncatccnt cnagtgctgn aaagccccnn cctgtctact tgtttggaga acngcnnnga 300
catgcccagn gttanataac nggcngagag tnantttgcc tctcccttcc ggctgcgcan 360
cgngtntgct tagnggacat aacctgacta cttaactgaa cccnngaatc tnccnccccct 420
ccactaagct cagaacaaaa aacttcgaca ccactcantt gtcacctgnc tgctcaagta 480
aagtgtaccc catncccaat gtntgctnga ngctctgncc tgcnttangt tcggtcctgg 540
gaagacctat caattnaagc tatgtttctg actgcctctt gctccctgna acaancnacc 600
cnncnntcca aggggggggnc ggcccccaat ccccccaacc ntnaattnan tttancccn 660
cccccnggcc cggcctttta cnancntcnn nnacngggna aaaccnnngc tttncccaac 720

nnaatccncc t 731

<210> 20
<211> 754
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(754)
<223> n = A,T,C or G

<400> 20
tttttttttt tttttttttt taaaaacccc ctccattnaa tgnaaacttc cgaaattgtc 60
caaccccctc ntccaaatnn ccntttccgg gngggggttc caaacccaan ttanntttgg 120
annttaaatt aaatnttnnt tggnggnnna anccnaatgt nangaaagtt naacccanta 180
tnancttnaa tncctggaaa ccngtngntt ccaaaaatnt ttaaccctta antccctccg 240
aaatngttna nggaaaaccc aanttctcnt aaggttgttt gaaggntnaa tnaaaanccc 300
nnccaattgt ttttngccac gcctgaatta attggnttcc gntgttttcc nttaaaanaa 360
ggnnancccc ggttantnaa tccccccnnc cccaattata ccgantttttt ttngaattgg 420
gancccncgg gaattaacgg ggnnnntccc tnttgggggg cnggnncccc cccentcggg 480
ggttngggnc aggncnnaat tgtttaaggg tccgaaaaat ccctccnaga aaaaaanctc 540
ccaggntgag nntngggttt ncccccccc canggcccct ctcgnanagt tggggtttgg 600
ggggcctggg atttntttc ccctnttncc tcccccccc ccngggganag aggttngngt 660
tttgntcnnc ggccccnccn aaganctttn ccganttnan ttaaatccnt gcctnggcga 720
agtccnttgn agggntaaan ggccccctnn cggg 754

<210> 21
<211> 755
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(755)
<223> n = A,T,C or G

<400> 21
atcancccat gaccccnaac nngggaccnc tcanccggnc nnncnaccnc cggccnatca 60
nngtnagnnc actncnnttn natcacnccc cnccnactac gcccncnanc cnacgcncta 120
nncanatncc actganngcg cgangtngan ngagaaanct nataccanag ncaccanacn 180
ccagctgtcc nanaangcct nnnatacngg nnnatccaat ntgnanccte cnaagtattn 240
nncnncanat gattttcctn anccgattac ccntnccccc tancccctcc cccccaacna 300
cgaaggcnct ggnccnaagg nngcgncncc ccgctagntc cccnncaagt cncncnccta 360
aactcanccn nattacncgc ttcntgagta tcactccccg aatctcaccc tactcaactc 420
aaaaanatcn gatacaaaat aatncaagcc tgnttatnac actntgactg ggtctctatt 480
ttagnggtcc ntnaancntc ctaatacttc cagtctnçct tcnccaattt ccnaanggct 540
ctttcngaca gcatnttttg gttcccnntt gggttcttan ngaattgccc ttcntngaac 600
gggctcntct tttccttcgg ttancctggn ttcnnccggc cagttattat ttcccntttt 660
aaattcntnc cntttantttt tggcnttcna aacccccggc cttgaaaacg gccccctggt 720
aaaaggttgt tttganaaaa tttttgtttt gttcc 755

<210> 22
<211> 849
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(849)
<223> n = A,T,C or G

<400> 22
```
tttttttttt tttttangtg tngtcgtgca ggtagaggct tactacaant gtgaanacgt      60
acgctnggan taangcgacc cganttctag gannencect aaaatcanac tgtgaagatn     120
atcctgnnna cggaanggtc accggnngat nntgctaggg tgnccnctcc cannnenttn     180
cataactcng nggccctgcc caccaccttc ggcggcccng ngnccgggcc cgggtcattn     240
gnnttaaccn cactnngcna ncggtttccn nccccnncng acccnggcga tccggggtnc     300
tctgtcttcc cctgnagncn anaaantggg ccncggnccc ctttacccct nnacaagcca     360
cngccntcta nccncngccc cccctccant nngggggact gccnanngct ccgttnctng     420
nnaccccnnn gggtncctcg gttgtcgant cnaccgnang ccanggattc cnaaggaagg     480
tgcgttnttg gcccctaccc ttcgctncgg nncacccttc ccgacnanga nccgctcccg     540
cncnncgnng cctcncctcg caacacccgc nctcntcngt ncggnnnccc ccccacccgc     600
nccctcncnc ngncgnancn ctccnccncc gtctcannca ccaccccgcc ccgccaggcc     660
ntcanccacn ggnngacnng nagcncnntc gcnccgcgcn gcgncnccct cgccncngaa     720
ctncntcngg ccantnncgc tcaanccnna cnaaacgccg ctgcgcggcc cgnagcgncc     780
ncctccncga gtcctcccgn cttccnaccc angnnttccn cgaggacacn nnaccccgcc     840
nncangcgg                                                             849
```

<210> 23
<211> 872
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(872)
<223> n = A,T,C or G

<400> 23
```
gcgcaaacta tacttcgctc gnactcgtgc gcctcgctnc tcttttcctc cgcaaccatg      60
tctgacnanc ccgattnggc ngatatcnan aagntcganc agtccaaact gantaacaca     120
cacacncnan aganaaatcc nctgccttcc anagtanacn attgaacnng agaaccangc     180
nggcgaatcg taatnaggcg tgcgccgcca atntgtcncc gtttattntn ccagcntcnc     240
ctnccnaccc tacntcttcn nagctgtcnn accccctngtn cgnacccccc naggtcggga     300
tcgggtttnn nntgaccgng cnnccccctcc cccentccat nacganccnc ccgcaccacc     360
nanngcncgc nccccgnnct cttcgccncc ctgtcctntn cccctgtngc ctggcncngn     420
accgcattga ccctcgccnn ctncnngaaa ncgnanacgt ccgggttgnn annancgctg     480
tgggnnngcg tctgcnccgc gttccttccn ncnncttcca ccatcttcnt tacngggtct     540
ccncgccntc tcnnncacnc cctgggacgc tntcctntgc ccccсttnac tcccccccctt     600
cgncgtgncc cgnccccacc ntcatttnca nacgntcttc acaannncct ggntnnctcc     660
cnancngncn gtcanccnag ggaagggngg ggnnccnntg nttgacgttg nggngangtc     720
cgaanantcc tcnccntcan cnctacccct cgggcgnnct ctcngttncc aacttancaa     780
ntctcccccg ngngcncntc tcagcctcnc ccnccccnct ctctgcantg tnctctgctc     840
tnaccnntac gantnttcgn cnccctcttt cc                                   872
```

<210> 24
<211> 815
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(815)
<223> n = A,T,C or G

<400> 24
gcatgcaagc ttgagtattc tatagngtca cctaaatanc ttggcntaat catggtcnta 60
nctgncttcc tgtgtcaaat gtatacnaan tanatatgaa tctnatntga caaganngta 120
tcntncatta gtaacaantg tnntgtccat cctgtcngan canattccca tnnattncgn 180
cgcattcncn gcncantatn taatngggaa ntcnnntnnn ncaccnncat ctatcntncc 240
gcncccctgac tggnagagat ggatnanttc tnntntgacc nacatgttca tcttggattn 300
aananccccc cgcngnccac cggttngnng cnagccnntc ccaagacctc ctgtggaggt 360
aacctgcgtc aganncatca aacntgggaa acccgcnncc angtnnaagt ngnnncanan 420
gatcccgtcc aggnttnacc atcccttcnc agcgccccct ttngtgcctt anagngnagc 480
gtgtccnanc cnctcaacat ganacgcgcc agnccanccg caattnggca caatgtcgnc 540
gaaccccccta gggggantna tncaaanccc caggattgtc cncncangaa atcccncanc 600
cccnccctac ccnnctttgg gacngtgacc aantcccgga gtnccagtcc ggccngnctc 660
ccccaccggt nnccntgggg gggtgaanct cngnntcanc cngncgaggn ntcgnaagga 720
accggncctn ggncgaanng ancnntcnga agngccncnt cgtataaccc cccctcncca 780
nccnacngnt agntcccccc cngggtncgg aangg 815

<210> 25
<211> 775
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(775)
<223> n = A,T,C or G

<400> 25
ccgagatgtc tcgctccgtg gccttagctg tgctcgcgct actctctctt tctggcctgg 60
aggctatcca gcgtactcca aagattcagg tttactcacg tcatccagca gagaatggaa 120
agtcaaattt cctgaattgc tatgtgtctg ggtttcatcc atccgacatt gaanttgact 180
tactgaagaa tgganagaga attgaaaaag tggagcattc agacttgtct ttcagcaagg 240
actggtcttt ctatctcntg tactacactg aattcacccc cactgaaaaa gatgagtatg 300
cctgccgtgt gaaccatgtg actttgtcac agcccaagat agttaagtgg gatcgagaca 360
tgtaagcagn cnncatggaa gtttgaagat gccgcatttg gattggatga attccaaatt 420
ctgcttgctt gcnttttaat antgatatgc ntatacaccc taccctttat gnccccaaat 480
tgtaggggtt acatnantgt tcncntngga catgatcttc ctttataant ccnccnttcg 540
aattgccccgt cncccngttn ngaatgtttc cnnaaccacg gttggctccc ccaggtcncc 600
tcttacggaa gggcctgggc cnctttncaa ggttggggga accnaaaatt tcncttntgc 660
ccncccncca cnntcttgng nncncanttt ggaacccttc cnattcccct tggcctcnna 720
nccttnncta anaaaacttn aaancgtngc naaannttttn acttcccccc ttacc 775

<210> 26
<211> 820
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(820)
<223> n = A,T,C or G

<400> 26
anattantac agtgtaatct tttcccagag gtgtgtanag ggaacggggc ctagaggcat 60
cccanagata ncttatanca acagtgcttt gaccaagagc tgctgggcac atttcctgca 120
gaaaaggtgg cggtccccat cactcctcct ctcccatagc catcccagag gggtgagtag 180
ccatcangcc ttcggtggga gggagtcang gaaacaacan accacagagc anacagacca 240
ntgatgacca tgggcgggag cgagcctctt ccctgnaccg gggtggcana nganagccta 300
nctgaggggt cacactataa acgttaacga ccnagatnan cacctgcttc aagtgcaccc 360

```
ttcctacctg acnaccagng accnnnaact gcngcctggg gacagcnctg gganc agcta     420
acnnagcact cacctgcccc cccatggccg tncgcntccc tggtcctgnc aagggaagct     480
ccctgttgga attncgggga naccaaggga ncccccctcct ccanctgtga aggaaaaann    540
gatggaattt tnccccttccg gccnntcccc tcttccttta cacgcccccct nntactcntc   600
tccctctntt ntcctgncnc acttttnacc ccnnnatttc ccttnattga tcggannctn     660
ganattccac tnncgcctnc cntcnatcng naaanacnaaa nactntctna cccnggggat    720
gggnncctcg ntcatcctct ctttttcnct accncccnntt ctttgcctct ccttngatca    780
tccaaccntc gntggccntn ccccccccnnn tcctttnccc                          820
```

<210> 27
<211> 818
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(818)
<223> n = A,T,C or G

<400> 27

```
tctgggtgat ggcctcttcc tcctcaggga cctctgactg ctctgggcca aagaatctct      60
tgtttcttct ccgagcccca ggcagcggtg attcagccct gcccaacctg attctgatga     120
ctgcggatgc tgtgacggac ccaaggggca aatagggtcc cagggtccag ggagggggcgc    180
ctgctgagca cttccgcccc tcaccctgcc cagcccctgc catgagctct gggctgggtc     240
tccgcctcca gggttctgct cttccangca ngccancaag tggcgctggg ccacactggc     300
ttcttcctgc cccntccctg gctctgantc tctgtcttcc tgtcctgtgc angcnccttg     360
gatctcagtt tccctcnctc anngaactct gtttctgann tcttcantta actntgantt     420
tatnaccnan tggnctgtnc tgtcnnactt taatgggccn gaccggctaa tccctccctc     480
nctcccttcc anttcnnnna accngcttnc cntcntctcc ccntancccg ccngggaanc     540
ctcctttgcc ctnaccangg gccnnnaccg cccntnnctn gggggggcnng gtnnctncnc   600
ctgntnnccc cnctcncnnt tncctcgtcc cnncnncgcn nngcannttc ncngtcccnn     660
tnnctcttcn ngtntcgnaa ngntcncntn tnnnnngncn ngntnntncn tccctctcnc     720
cnnntgnang tnnttnnnnc ncngnncccc nnnncnnnnn nggnnntnnn tctncncngc     780
cccnnccccc ngnattaagg cctccnntct ccggccnc                             818
```

<210> 28
<211> 731
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(731)
<223> n = A,T,C or G

<400> 28

```
aggaagggcg gagggatatt gtangggatt gagggatagg agnataangg gggaggtgtg      60
tcccaacatg anggtgnngt tctcttttga angagggttg ngtttttann ccnggtgggt     120
gattnaaccc cattgtatgg agnnaaaggn tttnagggat ttttcggctc ttatcagtat     180
ntanattcct gtnaatcgga aaatnatntt tcnncnggaa aatnttgctc ccatccgnaa     240
attnctcccg ggtagtgcat nttngggggn cngccangtt tcccaggctg ctanaatcgt     300
actaaagntt naagtgggan tncaaatgaa aacctnncac agagnatccn taccccgactg   360
tnnnttncct tcgccctntg actctgcnng agcccaatac ccnngngnat gtcnccccngn   420
nnngcgncnc tgaaannnnc tcgnggctnn gancatcang ggtttcgca tcaaaagcnn      480
cgtttcncat naaggcactt tngcctcatc caaccnctng ccctcnncca tttngccgtc     540
nggttcncct acgctnntng cncctnnntn ganattttnc ccgcctnggg naancctcct     600
gnaatgggta gggncttntc ttttnaccnn gnggtntact aatcnnctnc acgcntnctt     660
tctcnacccc ccccctttt caatcccanc ggcnaatggg gtctccccnn cgangggggg      720
```

```
nnncccannc c                                                          731

      <210> 29
      <211> 822
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(822)
      <223> n = A,T,C or G

      <400> 29
actagtccag tgtggtggaa ttccattgtg ttggggncnc ttctatgant antnttagat      60
cgctcanacc tcacanccctc ccnacnangc ctataangaa nannaataga nctgtncnnt    120
atntntacnc tcatanncct cnnnacccac tccctcttaa cccntactgt gcctatngcn     180
tnnctantct ntgccgcctn cnanccaccn gtgggccnac cncnngnatt ctcnatctcc     240
tcnccatntn gcctananta ngtncatacc ctatacctac nccaatgcta nnnctaancn     300
tccatnantt annntaacta ccactgacnt ngactttcnc atnanctcct aatttgaatc     360
tactctgact cccacngcct annnattagc ancntccccc nacnatntct caaccaaatc     420
ntcaacaacc tatctanctg ttcnccaacc nttncctccg atccccnnac aaccccccctc    480
ccaaataccc nccacctgac ncctaacccn caccatcccg gcaagccnan ggncatttan     540
ccactggaat cacnatngga naaaaaaaac ccnaactctc tancncnnat ctccctaana     600
aatnctcctn naatttactn ncantnccat caancccacn tgaaacnnaa cccctgtttt     660
tanatccctt ctttcgaaaa ccnaccccttt annncccaac ctttngggcc cccccnctnc    720
ccnaatgaag gncncccaat cnangaaacg nccntgaaaa ancnaggcna anannntccg     780
canatcctat cccttanttn ggggncccctt ncccngggcc cc                       822

      <210> 30
      <211> 787
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(787)
      <223> n = A,T,C or G

      <400> 30
cggccgcctg ctctggcaca tgcctcctga atggcatcaa aagtgatgga ctgcccattg      60
ctagagaaga ccttctctcc tactgtcatt atggagccct gcagactgag ggctcccctt     120
gtctgcagga tttgatgtct gaagtcgtgg agtgtggctt ggagctcctc atctacatna     180
gctggaagcc ctggagggcc tctctcgcca gcctccccct tctctccacg ctctccangg     240
acaccagggg ctccaggcag cccattattc ccagnangac atggtgtttc tccacgcgga     300
cccatggggc ctgnaaggcc agggtctcct ttgacaccat ctctcccgtc ctgcctggca     360
ggccgtggga tccactantt ctanaacggn cgccaccncg gtgggagctc cagcttttgt     420
tcccnttaat gaaggttaat tgcncgcttg gcgtaatcat nggtcanaac tntttcctgt     480
gtgaaattgt ttntcccctc ncnattccnc ncnacatacn aacccggaan cataaagtgt     540
taaagcctgg gggtngcctn nngaatnaac tnaactcaat taattgcgtt ggctcatggc     600
ccgctttccn ttcnggaaaa ctgtcntccc ctgcnttnnt gaatcggcca ccccccnggg     660
aaaagcggtt tgcnttttng ggggntcctt ccncttcccc cctcnctaan ccctncgcct     720
cggtcgttnc nggtngcggg gaangggnat nnnctcccnc naagggggng agnnngntat     780
ccccaaa                                                               787

      <210> 31
      <211> 799
      <212> DNA
      <213> Homo sapien
```

<220>
<221> misc_feature
<222> (1)...(799)
<223> n = A,T,C or G

<400> 31
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tttttttttt tttttttggc gatgctactg tttaattgca ggaggtgggg gtgtgtgtac      60
catgtaccag ggctattaga agcaagaagg aaggagggag ggcagagcgc cctgctgagc     120
aacaaaggac tcctgcagcc ttctctgtct gtctcttggc gcaggcacat ggggaggcct     180
cccgcagggt gggggccacc agtccagggg tgggagcact acanggggtg ggagtgggtg     240
gtggctggtn cnaatggcct gncacanatc cctacgattc ttgacacctg gatttcacca     300
ggggaccttc tgttctccca nggnaacttc ntnnatctcn aaagaacaca actgtttctt     360
cngcanttct ggctgttcat ggaaagcaca ggtgtccnat ttnggctggg acttggtaca     420
tatggttccg gcccacctct cccntcnaan aagtaattca cccccccccn ccntctnttg     480
cctgggccct taantaccca caccggaact canttantta ttcatcttng gntgggcttg     540
ntnatcnccn cctgaangcg ccaagttgaa aggccacgcc gtncccnctc cccatagnan     600
nttttnncnt canctaatgc ccccccnggc aacnatccaa tcccccccn tgggggcccc      660
agcccanggc ccccgnctcg ggnnnccngn cncgnantcc ccaggntctc ccantcngnc     720
ccnnngcncc cccgcacgca gaacanaagg ntngagccnc cgcannnnnn nggtnncnac     780
ctcgcccccc ccnncgnng                                                  799
```

<210> 32
<211> 789
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(789)
<223> n = A,T,C or G

<400> 32
```
tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt      60
ttttnccnag ggcaggttta ttgacaacct cncgggacac aancaggctg gggacaggac     120
ggcaacaggc tccggcggcg gcggcggcgg ccctacctgc ggtaccaaat ntgcagcctc     180
cgctcccgct tgatnttcct ctgcagctgc aggatgccnt aaaacagggc ctcggccntn     240
ggtgggcacc ctgggatttn aatttccacg ggcacaatgc ggtcgcancc cctcaccacc     300
nattaggaat agtggtntta cccnccnccg ttggcncact ccccntggaa accacttntc     360
gcggctccgg catctggtct taaaccttgc aaacnctggg gccctctttt tggttantnt     420
nccngccaca atcatnactc agactggcnc gggctggccc caaaaaancn ccccaaaacc     480
ggnccatgtc ttnncggggt tgctgcnatn tncatcacct cccgggcnca ncaggncaac     540
ccaaaagttc ttgnggcccn caaaaaanct ccgggggggnc ccagtttcaa caaagtcatc    600
ccccttggcc cccaaatcct ccccccgntt nctgggtttg ggaacccacg cctctnnctt     660
tggnnggcaa gntggntccc ccttcgggcc cccggtgggc ccnnctctaa ngaaaacncc     720
ntcctnnnca ccatcccccc nngnnacgnc tancaangna tccctttttt tanaaacggg     780
cccccncg                                                              789
```

<210> 33
<211> 793
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(793)
<223> n = A,T,C or G

<400> 33
gacagaacat gttggatggt ggagcacctt tctatacgac ttacaggaca gcagatgggg 60
aattcatggc tgttggagca atanaacccc agttctacga gctgctgatc aaaggacttg 120
gactaaagtc tgatgaactt cccaatcaga tgagcatgga tgattggcca gaaatgaana 180
agaagtttgc agatgtattt gcaaagaaga cgaaggcaga gtggtgtcaa atctttgacg 240
gcacagatgc ctgtgtgact ccggttctga cttttgagga ggttgttcat catgatcaca 300
acaangaacg ggctcgttt atcaccantg aggagcagga cgtgagcccc cgccctgcac 360
ctctgctgtt aaacacccca gccatccctt ctttcaaaag ggatccacta cttctagagc 420
ggncgccacc gcggtggagc tccagctttt gttcccttta gtgagggtta attgcgcgct 480
tggcgtaatc atggtcatan ctgtttcctg tgtgaaattg ttatccgctc acaattccac 540
acaacatacg anccggaagc atnaaatttt aaagcctggn ggtngcctaa tgantgaact 600
nactcacatt aattggcttt gcgctcactg cccgctttcc agtccggaaa acctgtcctt 660
gccagctgcc nttaatgaat cnggccaccc cccggggaaa aggcngtttg cttnttgggg 720
cgcncttccc gctttctcgc ttcctgaant ccttcccccc ggtctttcgg cttgcggcna 780
acggtatcna cct 793

<210> 34
<211> 756
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(756)
<223> n = A,T,C or G

<400> 34
gccgcgaccg gcatgtacga gcaactcaag ggcgagtgga accgtaaaag ccccaatctt 60
ancaagtgcg gggaanagct gggtcgactc aagctagttc ttctggagct caacttcttg 120
ccaaccacag ggaccaagct gaccaaacag cagctaattc tggcccgtga catactggag 180
atcggggccc aatggagcat cctacgcaan gacatcccct ccttcgagcg ctacatggcc 240
cagctcaaat gctactactt tgattacaan gagcagctcc ccgagtcagc ctatatgcac 300
cagctcttgg gcctcaacct cctcttcctg ctgtcccaga accgggtggc tgantnccac 360
acgganttgg ancggctgcc tgcccaanga catacanacc aatgtctaca tcnaccacca 420
gtgtcctgga gcaatactga tgganggcag ctaccncaaa gtnttcctgg ccnagggtaa 480
catcccccgc cgagagctac accttcttca ttgacatcct gctcgacact atcagggatg 540
aaaatcgcng ggttgctcca gaaaggctnc aanaanatcc ttttcnctga aggcccccgg 600
atncnctagt nctagaatcg gcccgccatc gcggtgganc ctccaacctt tcgttnccct 660
ttactgaggg ttnattgccg cccttggcgt tatcatggtc acnccngttn cctgtgttga 720
aattnttaac cccccacaat tccacgccna cattng 756

<210> 35
<211> 834
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(834)
<223> n = A,T,C or G

<400> 35
ggggatctct anatcnacct gnatgcatgg ttgtcggtgt ggtcgctgtc gatgaanatg 60
aacaggatct tgcccttgaa gctctcggct gctgtnttta agttgctcag tctgccgtca 120
tagtcagaca cnctcttggg caaaaaacan caggatntga gtcttgattt cacctccaat 180
aatcttcngg gctgtctgct cggtgaactc gatgacnang ggcagctggt tgtgtntgat 240
aaantccanc angttctcct tggtgacctc cccttcaaag ttgttccggc cttcatcaaa 300
cttctnnaan angannancc canctttgtc gagctggnat ttgganaaca cgtcactgtt 360

```
ggaaactgat cccaaatggt atgtcatcca tcgcctctgc tgcctgcaaa aaacttgctt     420
ggcncaaatc cgactccccn tccttgaaag aagccnatca cacccccctc cctggactcc     480
nncaangact ctnccgctnc cccntccnng cagggttggt ggcanncçgg gcccntgcgc     540
ttcttcagcc agttcacnat nttcatcagc ccctctgcca gctgttntat tccttggggg     600
ggaanccgtc tctcccttcc tgaannaact ttgaccgtng gaatagccgc gcntcnccnt     660
acntnctggg ccgggttcaa antccctccn ttgncnntcn cctcgggcca ttctggattt     720
nccnaacttt ttccttcccc cnccccncgg ngtttggntt tttcatnggg ccccaactct     780
gctnttggcc antcccctgg gggcntntan cnccccctnt ggtcccntng ggcc           834

      <210> 36
      <211> 814
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(814)
      <223> n = A,T,C or G

      <400> 36
cggncgcttt ccngccgcgc cccgtttcca tgacnaaggc tcccttcang ttaaatacnn      60
cctagnaaac attaatgggt tgctctacta atacatcata cnaaccagta agcctgccca     120
naacgccaac tcaggccatt cctaccaaag gaagaaaggc tggtctctcc accccctgta     180
ggaaaggcct gccttgtaag acaccacaat ncggctgaat ctnaagtctt gtgttttact     240
aatggaaaaa aaaaataaac aanaggtttt gttctcatgg ctgcccaccg cagcctggca     300
ctaaaacanc ccagcgctca cttctgcttg ganaaatatt ctttgctctt ttggacatca     360
ggcttgatgg tatcactgcc acntttccac ccagctgggc nccccttcccc catntttgtc    420
antganctgg aaggcctgaa ncttagtctc caaaagtctc ngcccacaag accggccacc     480
aggggangtc ntttncagtg gatctgccaa anantacccn tatcatcnnt gaataaaaag     540
gcccctgaac ganatgcttc cancanccctt taagacccat aatcctngaa ccatggtgcc    600
cttccggtct gatccnaaag gaatgttcct gggtcccant ccctcctttg ttncttacgt     660
tgtnttggac ccntgctngn atnacccaan tganatcccc ngaagcaccc tnccccctggc    720
atttganttt cntaaattct ctgccctacn nctgaaagca cnattccctn ggcnccnaan     780
ggngaactca agaaggtctn ngaaaaacca cncn                                 814

      <210> 37
      <211> 760
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(760)
      <223> n = A,T,C or G

      <400> 37
gcatgctgct cttcctcaaa gttgttcttg ttgccataac aaccaccata ggtaaagcgg      60
gcgcagtgtt cgctgaaggg gttgtagtac cagcgcggga tgctctcctt gcagagtcct     120
gtgtctggca ggtccacgca atgccctttg tcactgggga aatggatgcg ctggagctcg     180
tcnaanccac tcgtgtattt ttcacangca gcctcctccg aagcntccgg gcagttgggg     240
gtgtcgtcac actccactaa actgtcgatn cancagccca ttgctgcagc ggaactgggt     300
gggctgacag gtgccagaac acactggatn ggcctttcca tggaagggcc tgggggaaat     360
cncctnancc caaactgcct ctcaaaggcc accttgcaca ccccgacagg ctagaaatgc     420
actcttcttc ccaaaggtag ttgttcttgt tgcccaagca ncctccanca aaccaaaanc     480
ttgcaaaatc tgctccgtgg gggtcatnnn taccanggtt ggggaaanaa acccggcngn     540
ganccncctt gtttgaatgc naaggnaata atcctcctgt cttgcttggg tggaanagca     600
caattgaact gttaacnttg ggccgngttc cnctngggtg gtctgaaact aatcaccgtc     660
actggaaaaa ggtangtgcc ttccttgaat tcccaaantt cccctngntt tgggtnnttt     720
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ctcctctncc ctaaaaatcg tnttcccccc ccntanggcg 760

<210> 38
<211> 724
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(724)
<223> n = A,T,C or G

<400> 38
tttttttttt tttttttttt tttttttttt tttttaaaaa ccccctccat tgaatgaaaa 60
cttccnaaat tgtccaaccc cctcnnccaa atnnccattt ccgggggggg gttccaaacc 120
caaattaatt ttgganttta aattaaatnt tnattngggg aanaanccaa atgtnaagaa 180
aatttaaccc attatnaact taaatncctn gaaacccntg gnttccaaaa atttttaacc 240
cttaaatccc tccgaaattg ntaanggaaa accaaattcn cctaaggctn tttgaaggtt 300
ngatttaaac cccсttnant tnttttnacc cnngnctnaa ntatttngnt tccggtgttt 360
tcctnttaan cntnggtaac tcccgntaat gaannncccct aanccaatta aaccgaattt 420
tttttgaatt ggaaattccn ngggaattna ccggggtttt tcccntttgg gggccatncc 480
cccnctttcg gggtttgggn ntaggttgaa tttttnnang ncccaaaaaa ncccccaana 540
aaaaaactcc caagnnttaa ttngaatntc cccсttccca ggccttttgg gaaaggnggg 600
tttntggggg ccngggantt cnttcccccn ttnccncccc cccccсnggt aaanggttat 660
ngnntttggt ttttgggccc cttnanggac cttccggatn gaaattaaat ccccgggncg 720
gccg 724

<210> 39
<211> 751
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(751)
<223> n = A,T,C or G

<400> 39
tttttttttt tttttctttg ctcacattta atttttattt tgattttttt taatgctgca 60
caacacaata tttatttcat ttgtttcttt tatttcattt tatttgtttg ctgctgctgt 120
tttatttatt tttactgaaa gtgagaggga actttttgtgg cctttttttcc tttttctgta 180
ggccgcctta agctttctaa atttggaaca tctaagcaag ctgaanggaa aagggggttt 240
cgcaaaatca ctcgggggaa nggaaaggtt gctttgttaa tcatgcccta tggtgggtga 300
ttaactgctt gtacaattac ntttcacttt taattaattg tgctnaangc tttaattana 360
cttgggggtt ccctccccan accaaccccn ctgacaaaaa gtgccngccc tcaaatnatg 420
tcccggcnnt cnttgaaaca cacngcngaa ngttctcatt ntccccncnc caggtnaaaa 480
tgaagggtta ccatntttaa cnccacctcc acntggcnnn gcctgaatcc tcnaaaancn 540
ccctcaancn aattnctnng ccccggtcnc gcntnngtcc cnccccgggct ccgggaantn 600
caccccccnga anncnntnnc naacnaaatt ccgaaaatat tcccnntcnc tcaattcccc 660
cnnagactnt cctcnncnan cncaattttc ttttnntcac gaacncgnnc cnnaaaatgn 720
nnnncncctc cnctngtccn naatcnccan c 751

<210> 40
<211> 753
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(753)
<223> n = A,T,C or G

<400> 40
gtggtatttt ctgtaagatc aggtgttcct ccctcgtagg tttagaggaa acaccctcat 60
agatgaaaac ccccccgaga cagcagcact gcaactgcca agcagccggg gtaggagggg 120
cgccctatgc acagctgggc ccttgagaca gcagggcttc gatgtcaggc tcgatgtcaa 180
tggtctggaa gcggcggctg tacctgcgta ggggcacacc gtcagggccc accaggaact 240
tctcaaagtt ccaggcaacn tcgttgcgac acaccggaga ccaggtgatn agcttggggt 300
cggtcataan cgcggtggcg tcgtcgctgg gagctggcag ggcctcccgc aggaaggcna 360
ataaaaggtg cgcccccgca ccgttcanct cgcacttctc naanaccatg angttgggct 420
cnaacccacc accannccgg acttccttga nggaattccc aaatctcttc gntcttgggc 480
ttctnctgat gccctanctg gttgcccngn atgccaanca nccccaancc ccggggtcct 540
aaancacccn cctcctcntt tcatctgggt tnttntcccc ggaccntggt tcctctcaag 600
gganccccata tctcnaccan tactcaccnt ncccccccnt gnnacccanc cttctanngn 660
ttcccncccg ncctctggcc cntcaaanan gcttncacna cctgggtctg ccttcccccc 720
tnccctatct gnaccccncn tttgtctcan tnt 753

<210> 41
<211> 341
<212> DNA
<213> Homo sapien

<400> 41
actatatcca tcacaacaga catgcttcat cccatagact tcttgacata gcttcaaatg 60
agtgaaccca tccttgattt atatacatat atgttctcag tattttggga gcctttccac 120
ttctttaaac cttgttcatt atgaacactg aaaataggaa tttgtgaaga gttaaaaagt 180
tatagcttgt ttacgtagta agtttttgaa gtctacattc aatccagaca cttagttgag 240
tgttaaactg tgatttttaa aaaatatcat ttgagaatat tctttcagag gtattttcat 300
ttttactttt tgattaattg tgttttatat attagggtag t 341

<210> 42
<211> 101
<212> DNA
<213> Homo sapien

<400> 42
acttactgaa tttagttctg tgctcttcct tatttagtgt tgtatcataa atactttgat 60
gtttcaaaca ttctaaataa ataattttca gtggcttcat a 101

<210> 43
<211> 305
<212> DNA
<213> Homo sapien

<400> 43
acatctttgt tacagtctaa gatgtgttct taaatcacca ttccttcctg gtcctcaccc 60
tccagggtgg tctcacactg taattagagc tattgaggag tctttacagc aaattaagat 120
tcagatgcct tgctaagtct agagttctag agttatgttt cagaaagtct aagaaaccca 180
cctcttgaga ggtcagtaaa gaggacttaa tatttcatat ctacaaaatg accacaggat 240
tggatacaga acgagagtta tcctggataa ctcagagctg agtacctgcc cgggggccgc 300
tcgaa 305

<210> 44
<211> 852
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(852)
<223> n = A,T,C or G

<400> 44
acataaatat cagagaaaag tagtctttga aatatttacg tccaggagtt ctttgtttct 60
gattatttgg tgtgtgtttt ggtttgtgtc caaagtattg gcagcttcag ttttcatttt 120
ctctccatcc tcgggcattc ttcccaaatt tatataccag tcttcgtcca tccacacgct 180
ccagaatttc tcttttgtag taatatctca tagctcggct gagcttttca taggtcatgc 240
tgctgttgtt cttcttttta ccccatagct gagccactgc ctctgatttc aagaacctga 300
agacgccctc agatcggtct tcccatttta ttaatcctgg gttcttgtct gggttcaaga 360
ggatgtcgcg gatgaattcc cataagtgag tccctctcgg gttgtgcttt ttggtgtggc 420
acttggcagg ggggtcttgc tcctttttca tatcaggtga ctctgcaaca ggaaggtgac 480
tggtggttgt catggagatc tgagcccggc agaaagtttt gctgtccaac aaatctactg 540
tgctaccata gttggtgtca tataaatagt tctngtcttt ccaggtgttc atgatggaag 600
gctcagtttg ttcagtcttg acaatgacat tgtgtgtgga ctggaacagg tcactactgc 660
actggccgtt ccacttcaga tgctgcaagt tgctgtagag gagntgcccc gccgtccctg 720
ccgcccgggt gaactcctgc aaactcatgc tgcaaaggtg ctcgccgttg atgtcgaact 780
cntggaaagg gatacaattg gcatccagct ggttggtgtc caggaggtga tggagccact 840
cccacacctg gt 852

<210> 45
<211> 234
<212> DNA
<213> Homo sapien

<400> 45
acaacagacc cttgctcgct aacgacctca tgctcatcaa gttggacgaa tccgtgtccg 60
agtctgacac catccggagc atcagcattg cttcgcagtg ccctaccgcg gggaactctt 120
gcctcgtttc tggctggggt ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg 180
tgaacgtgtc ggtggtgtct gaggaggtct gcagtaagct ctatgacccg ctgt 234

<210> 46
<211> 590
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(590)
<223> n = A,T,C or G

<400> 46
actttttatt taaatgttta taaggcagat ctatgagaat gatagaaaac atggtgtgta 60
atttgatagc aatattttgg agattacaga gttttagtaa ttaccaatta cacagttaaa 120
aagaagataa tatattccaa gcanatacaa aatatctaat gaaagatcaa ggcaggaaaa 180
tgantataac taattgacaa tggaaaatca attttaatgt gaattgcaca ttatccttta 240
aaagctttca aaanaaanaa ttattgcagt ctanttaatt caaacagtgt taaatggtat 300
caggataaan aactgaaggg canaaagaat taattttcac ttcatgtaac ncacccanat 360
ttacaatggc ttaaatgcan ggaaaaagca gtggaagtag ggaagtantc aaggtctttc 420
tggtctctaa tctgccttac tctttgggtg tggctttgat cctctggaga cagctgccag 480
ggctcctgtt atatccacaa tcccagcagc aagatgaagg gatgaaaaag gacacatgct 540
gccttccttt gaggagactt catctcactg gccaacactc agtcacatgt 590

<210> 47
<211> 774

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(774)
<223> n = A,T,C or G

<400> 47
acaagggggc ataatgaagg agtggggana gattttaaag aaggaaaaaa aacgaggccc 60
tgaacagaat tttcctgnac aacggggctt caaaataatt ttcttgggga ggttcaagac 120
gcttcactgc ttgaaactta aatggatgtg ggacanaatt ttctgtaatg accctgaggg 180
cattacagac gggactctgg gaggaaggat aaacagaaag gggacaaagg ctaatcccaa 240
aacatcaaag aaaggaaggt ggcgtcatac ctcccagcct acacagttct ccagggctct 300
cctcatccct ggaggacgac agtggaggaa caactgacca tgtccccagg ctcctgtgtg 360
ctggctcctg gtcttcagcc cccagctctg gaagcccacc ctctgctgat cctgcgtggc 420
ccacactcct tgaacacaca tccccaggtt atattcctgg acatggctga acctcctatt 480
cctacttccg agatgccttg ctccctgcag cctgtcaaaa tcccactcac cctccaaacc 540
acggcatggg aagcctttct gacttgcctg attactccag catcttggaa caatccctga 600
ttccccactc cttagaggca agatagggtg gttaagagta gggctggacc acttggagcc 660
aggctgctgg cttcaaattn tggctcattt acgagctatg ggaccttggg caagtnatct 720
tcacttctat gggcntcatt ttgttctacc tgcaaaatgg gggataataa tagt 774

<210> 48
<211> 124
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(124)
<223> n = A,T,C or G

<400> 48
canaaattga aattttataa aaaggcattt ttctcttata tccataaaat gatataattt 60
ttgcaantat anaaatgtgt cataaattat aatgttcctt aattacagct caacgcaact 120
tggt 124

<210> 49
<211> 147
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(147)
<223> n = A,T,C or G

<400> 49
gccgatgcta ctattttatt gcaggaggtg ggggtgtttt tattattctc tcaacagctt 60
tgtggctaca ggtggtgtct gactgcatna aaaanttttt tacgggtgat tgcaaaaatt 120
ttagggcacc catatcccaa gcantgt 147

<210> 50
<211> 107
<212> DNA
<213> Homo sapien

<400> 50
acattaaatt aataaaagga ctgttggggt tctgctaaaa cacatggctt gatatattgc 60
atggtttgag gttaggagga gttaggcata tgttttggga gaggggt 107

<210> 51
<211> 204
<212> DNA
<213> Homo sapien

<400> 51
gtcctaggaa gtctagggga cacacgactc tggggtcacg gggccgacac acttgcacgg 60
cgggaaggaa aggcagagaa gtgacaccgt caggggggaaa tgacagaaag gaaaatcaag 120
gccttgcaag gtcagaaagg ggactcaggg cttccaccac agccctgccc cacttggcca 180
cctccctttt gggaccagca atgt 204

<210> 52
<211> 491
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(491)
<223> n = A,T,C or G

<400> 52
acaaagataa catttatctt ataacaaaaa tttgatagtt ttaaaggtta gtattgtgta 60
gggtattttc caaaagacta aagagataac tcaggtaaaa agttagaaat gtataaaaca 120
ccatcagaca ggtttttaaa aaacaacata ttacaaaatt agacaatcat ccttaaaaaa 180
aaaacttctt gtatcaattt cttttgttca aaatgactga cttaantatt tttaaatatt 240
tcanaaacac ttcctcaaaa attttcaana tggtagcttt canatgtncc ctcagtccca 300
atgttgctca gataaataaa tctcgtgaga acttaccacc caccacaagc tttctggggc 360
atgcaacagt gtcttttctt tnctttttct tttttttttt ttacaggcac agaaactcat 420
caattttatt tggataacaa agggtctcca aattatattg aaaaataaat ccaagttaat 480
atcactcttg t 491

<210> 53
<211> 484
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(484)
<223> n = A,T,C or G

<400> 53
acataattta gcagggctaa ttaccataag atgctattta ttaanaggtn tatgatctga 60
gtattaacag ttgctgaagt ttggtatttt tatgcagcat tttctttttg ctttgataac 120
actacagaac ccttaaggac actgaaaatt agtaagtaaa gttcagaaac attagctgct 180
caatcaaatc tctacataac actatagtaa ttaaaacgtt aaaaaaaagt gttgaaatct 240
gcactagtat anaccgctcc tgtcaggata anactgcttt ggaacagaaa gggaaaaanc 300
agctttgant ttctttgtgc tgatangagg aaaggctgaa ttaccttgtt gcctctccct 360
aatgattggc aggtcnggta aatnccaaaa catattccaa ctcaacactt cttttccncg 420
tancttgant ctgtgtattc cagganc agg cggatggaat gggccagccc ncggatgttc 480
cant 484

<210> 54

<211> 151
<212> DNA
<213> Homo sapien

<400> 54
actaaacctc gtgcttgtga actccataca gaaaacggtg ccatccctga acacggctgg 60
ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag 120
tctatgtcct ctcaagtgcc tttttgtttg t 151

<210> 55
<211> 91
<212> DNA
<213> Homo sapien

<400> 55
acctggcttg tctccgggtg gttcccggcg ccccccacgg tccccagaac ggacactttc 60
gccctccagt ggatactcga gccaaagtgg t 91

<210> 56
<211> 133
<212> DNA
<213> Homo sapien

<400> 56
ggcggatgtg cgttggttat atacaaatat gtcattttat gtaagggact tgagtatact 60
tggatttttg gtatctgtgg gttgggggga cggtccagga accaataccc catggatacc 120
aagggacaac tgt 133

<210> 57
<211> 147
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(147)
<223> n = A,T,C or G

<400> 57
actctggaga acctgagccg ctgctccgcc tctgggatga ggtgatgcan gcngtggcgc 60
gactgggagc tgagcccttc cctttgcgcc tgcctcagag gattgttgcc gacntgcana 120
tctcantggg ctggatncat gcagggt 147

<210> 58
<211> 198
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(198)
<223> n = A,T,C or G

<400> 58
acagggatat aggtttnaag ttattgtnat tgtaaaatac attgaatttt ctgtatactc 60
tgattacata catttatcct ttaaaaaaga tgtaaatctt aatttttatg ccatctatta 120
atttaccaat gagttacctt gtaaatgaga agtcatgata gcactgaatt ttaactagtt 180
ttgacttcta agtttggt 198

<210> 59
<211> 330
<212> DNA
<213> Homo sapien

<400> 59
acaacaaatg ggttgtgagg aagtcttatc agcaaaactg gtgatggcta ctgaaaagat 60
ccattgaaaa ttatcattaa tgattttaaa tgacaagtta tcaaaaactc actcaatttt 120
cacctgtgct agcttgctaa aatgggagtt aactctagag caaatatagt atcttctgaa 180
tacagtcaat aaatgacaaa gccagggcct acaggtggtt tccagacttt ccagacccag 240
cagaaggaat ctattttatc acatggatct ccgtctgtgc tcaaaatacc taatgatatt 300
tttcgtcttt attggacttc tttgaagagt 330

<210> 60
<211> 175
<212> DNA
<213> Homo sapien

<400> 60
accgtgggtg ccttctacat tcctgacggc tccttcacca acatctggtt ctacttcggc 60
gtcgtgggct ccttcctctt catcctcatc cagctggtgc tgctcatcga ctttgcgcac 120
tcctggaacc agcggtggct gggcaaggcc gaggagtgcg attcccgtgc ctggt 175

<210> 61
<211> 154
<212> DNA
<213> Homo sapien

<400> 61
accccacttt tcctcctgtg agcagtctgg acttctcact gctacatgat gagggtgagt 60
ggttgttgct cttcaacagt atcctcccct ttccggatct gctgagccgg acagcagtgc 120
tggactgcac agccccgggg ctccacattg ctgt 154

<210> 62
<211> 30
<212> DNA
<213> Homo sapien

<400> 62
cgctcgagcc ctatagtgag tcgtattaga 30

<210> 63
<211> 89
<212> DNA
<213> Homo sapien

<400> 63
acaagtcatt tcagcaccct ttgctcttca aaactgacca tcttttatat ttaatgcttc 60
ctgtatgaat aaaaatggtt atgtcaagt 89

<210> 64
<211> 97
<212> DNA
<213> Homo sapien

<400> 64
accggagtaa ctgagtcggg acgctgaatc tgaatccacc aataaataaa ggttctgcag 60

aatcagtgca tccaggattg gtccttggat ctggggt 97

<210> 65
<211> 377
<212> DNA
<213> *Homo sapien*

<220>
<221> misc_feature
<222> (1)...(377)
<223> n = A,T,C or G

<400> 65
acaacaanaa ntcccttctt taggccactg atggaaacct ggaaccccct tttgatggca 60
gcatggcgtc ctaggccttg acacagcggc tggggtttgg gctntcccaa accgcacacc 120
ccaaccctgg tctacccaca nttctggcta tgggctgtct ctgccactga acatcagggt 180
tcggtcataa natgaaatcc caanggggac agaggtcagt agaggaagct caatgagaaa 240
ggtgctgttt gctcagccag aaaacagctg cctggcattc gccgctgaac tatgaacccg 300
tgggggtgaa ctacccccan gaggaatcat gcctgggcga tgcaanggtg ccaacaggag 360
gggcgggagg agcatgt 377

<210> 66
<211> 305
<212> DNA
<213> Homo sapien

<400> 66
acgcctttcc ctcagaattc agggaagaga ctgtcgcctg ccttcctccg ttgttgcgtg 60
agaacccgtg tgccccttcc caccatatcc accctcgctc catctttgaa ctcaaacacg 120
aggaactaac tgcaccctgg tcctctcccc agtccccagt tcaccctcca tccctcacct 180
tcctccactc taagggatat caacactgcc cagcacaggg gccctgaatt tatgtggttt 240
ttatatattt tttaataaga tgcactttat gtcatttttt aataaagtct gaagaattac 300
tgttt 305

<210> 67
<211> 385
<212> DNA
<213> Homo sapien

<400> 67
actacacaca ctccacttgc ccttgtgaga cactttgtcc cagcacttta ggaatgctga 60
ggtcggacca gccacatctc atgtgcaaga ttgcccagca gacatcaggt ctgagagttc 120
ccctttttaaa aaaggggact tgcttaaaaa agaagtctag ccacgattgt gtagagcagc 180
tgtgctgtgc tggagattca cttttgagag agttctcctc tgagacctga tctttagagg 240
ctgggcagtc ttgcacatga gatggggctg gtctgatctc agcactcctt agtctgcttg 300
cctctcccag ggccccagcc tggccacacc tgcttacagg gcactctcag atgcccatac 360
catagtttct gtgctagtgg accgt 385

<210> 68
<211> 73
<212> DNA
<213> Homo sapien

<400> 68
acttaaccag atatattttt accccagatg gggatattct ttgtaaaaaa tgaaaataaa 60
gtttttttaa tgg 73

<210> 69

<211> 536
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(536)
<223> n = A,T,C or G

<400> 69
```
actagtccag tgtggtggaa ttccattgtg ttgggggctc tcaccctcct ctcctgcagc     60
tccagctttg tgctctgcct ctgaggagac catggcccag catctgagta ccctgctgct    120
cctgctggcc accctagctg tggccctggc ctggagcccc aaggaggagg ataggataat    180
cccgggtggc atctataacg cagacctcaa tgatgagtgg gtacagcgtg cccttcactt    240
cgccatcagc gagtataaca aggccaccaa agatgactac tacagacgtc cgctgcgggt    300
actaagagcc aggcaacaga ccgttggggg ggtgaattac ttcttcgacg tagaggtggg    360
ccgaaccata tgtaccaagt cccagcccaa cttggacacc tgtgccttcc atgaacagcc    420
agaactgcag aagaaacagt tgtgctcttt cgagatctac gaagttccct ggggagaaca    480
gaangtccct gggtgaaatc caggtgtcaa gaaatcctan ggatctgttg ccaggc        536
```

<210> 70
<211> 477
<212> DNA
<213> Homo sapien

<400> 70
```
atgaccccta acaggggccc tctcagccct cctaatgacc tccggcctag ccatgtgatt     60
tcacttccac tccataacgc tcctcatact aggcctacta accaacacac taaccatata    120
ccaatgatgg cgcgatgtaa cacgagaaag cacataccaa ggccaccaca caccacctgt    180
ccaaaaaggc cttcgatacg ggataatcct atttattacc tcagaagttt ttttcttcgc    240
agggattttt ctgagccttt taccactcca gcctagcccc taccccccaa ctaggagggc    300
actggccccc aacaggcatc accccgctaa atcccctaga agtcccactc ctaaacacat    360
ccgtattact cgcatcagga gtatcaatca cctgagctca ccatagtcta atagaaaaca    420
accgaaacca aattattcaa agcactgctt attacaattt tactgggtct ctatttt       477
```

<210> 71
<211> 533
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(533)
<223> n = A,T,C or G

<400> 71
```
agagctatag gtacagtgtg atctcagctt tgcaaacaca ttttctacat agatagtact     60
aggtattaat agatatgtaa agaaagaaat cacaccatta ataatggtaa gattggttta    120
tgtgatttta gtggtatttt tggcaccctt atatatgttt tccaaacttt cagcagtgat    180
attatttcca taacttaaaa agtgagtttg aaaaagaaaa tctccagcaa gcatctcatt    240
taaataaagg tttgtcatct ttaaaaatac agcaatatgt gactttttaa aaaagctgtc    300
aaataggtgt gaccctacta ataattatta gaaatacatt taaaaacatc gagtacctca    360
agtcagtttg ccttgaaaaa tatcaaatat aactcttaga gaaatgtaca taaaagaatg    420
cttcgtaatt ttggagtang aggttccctc ctcaatttg tatttttaaa aagtacatgg     480
taaaaaaaaa aattcacaac agtatataag gctgtaaaat gaagaattct gcc           533
```

<210> 72
<211> 511

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 72
```
tattacggaa aaacacacca cataattcaa ctancaaaga anactgcttc agggcgtgta    60
aaatgaaagg cttccaggca gttatctgat taaagaacac taaaagaggg acaaggctaa   120
aagccgcagg atgtctacac tatancaggc gctatttggg ttggctggag gagctgtgga   180
aaacatggan agattggtgc tgganatcgc cgtggctatt cctcattgtt attacanagt   240
gaggttctct gtgtgcccac tggtttgaaa accgttctnc aataatgata gaatagtaca   300
cacatgagaa ctgaaatggc ccaaacccag aaagaaagcc caactagatc ctcagaanac   360
gcttctaggg acaataaccg atgaagaaaa gatggcctcc ttgtgccccc gtctgttatg   420
atttctctcc attgcagcna naaacccgtt cttctaagca aacncaggtg atgatggcna   480
aaatacaccc cctcttgaag naccnggagg a                                  511
```

<210> 73
<211> 499
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(499)
<223> n = A,T,C or G

<400> 73
```
cagtgccagc actggtgcca gtaccagtac caataacagt gccagtgcca gtgccagcac    60
cagtggtggc ttcagtgctg gtgccagcct gaccgccact ctcacatttg ggctcttcgc   120
tggccttggt ggagctggtg ccagcaccag tggcagctct ggtgcctgtg gtttctccta   180
caagtgagat tttagatatt gttaatcctg ccagtctttc tcttcaagcc agggtgcatc   240
ctcagaaacc tactcaacac agcactctag gcagccacta tcaatcaatt gaagttgaca   300
ctctgcatta aatctatttg ccatttctga aaaaaaaaaa aaaaaaaggg cggccgctcg   360
antctagagg gcccgtttaa acccgctgat cagcctcgac tgtgccttct anttgccagc   420
catctgttgt ttgcccctcc cccgntgcct tccttgaccc tggaaagtgc cactcccact   480
gtcctttcct aantaaaat                                                499
```

<210> 74
<211> 537
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(537)
<223> n = A,T,C or G

<400> 74
```
tttcatagga gaacacactg aggagatact tgaagaattt ggattcagcc gcgaagagat    60
ttatcagctt aactcagata aaatcattga aagtaataag gtaaaagcta gtctctaact   120
tccaggccca cggctcaagt gaatttgaat actgcattta cagtgtagag taacacataa   180
cattgtatgc atggaaacat ggaggaacag tattacagtg tcctaccact ctaatcaaga   240
aaagaattac agactctgat tctacagtga tgattgaatt ctaaaaatgg taatcattag   300
ggcttttgat ttataanact ttgggtactt atactaaatt atggtagtta tactgccttc   360
cagtttgctt gatatatttg ttgatattaa gattcttgac ttatattttg aatgggttct   420
```

```
actgaaaaan gaatgatata ttcttgaaga catcgatata catttattta cactcttgat     480
tctacaatgt agaaaatgaa ggaaatgccc caaattgtat ggtgataaaa gtcccgt        537
```

<210> 75
<211> 467
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(467)
<223> n = A,T,C or G

<400> 75

```
caaanacaat tgttcaaaag atgcaaatga tacactactg ctgcagctca caaacacctc      60
tgcatattac acgtacctcc tcctgctcct caagtagtgt ggtctatttt gccatcatca     120
cctgctgtct gcttagaaga acggctttct gctgcaangg agagaaatca taacagacgg     180
tggcacaagg aggccatctt ttcctcatcg gttattgtcc ctagaagcgt cttctgagga     240
tctagttggg ctttctttct gggtttgggc catttcantt ctcatgtgtg tactattcta     300
tcattattgt ataacggttt tcaaaccngt gggcacncag agaacctcac tctgtaataa     360
caatgaggaa tagccacggt gatctccagc accaaatctc tccatgttnt tccagagctc     420
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn                   467
```

<210> 76
<211> 400
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(400)
<223> n = A,T,C or G

<400> 76

```
aagctgacag cattcgggcc gagatgtctc gctccgtggc cttagctgtg ctcgcgctac      60
tctctctttc tggcctggag gctatccagc gtactccaaa gattcaggtt tactcacgtc     120
atccagcaga gaatggaaag tcaaatttcc tgaattgcta tgtgtctggg tttcatccat     180
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaagtg gagcattcag     240
acttgtcttt cagcaaggac tggtctttct atctcttgta ctacactgaa ttcaccccca     300
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng     360
ttnagtggga tcganacatg taagcagcan catgggaggt                           400
```

<210> 77
<211> 248
<212> DNA
<213> Homo sapien

<400> 77

```
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct      60
ccagctgccc cggcggggga tgcgaggctc ggagcaccct tgcccggctg tgattgctgc     120
caggcactgt tcatctcagc ttttctgtcc ctttgctccc ggcaagcgct tctgctgaaa     180
gttcatatct ggagcctgat gtcttaacga ataaaggtcc catgctccac ccgaaaaaaa     240
aaaaaaaa                                                              248
```

<210> 78
<211> 201
<212> DNA
<213> Homo sapien

<400> 78
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca 60
tcacccagac cccgccctgc ccgtgcccca cgctgctgct aacgacagta tgatgcttac 120
tctgctactc ggaaactatt tttatgtaat taatgtatgc tttcttgttt ataaatgcct 180
gatttaaaaa aaaaaaaaaa a 201

<210> 79
<211> 552
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(552)
<223> n = A,T,C or G

<400> 79
tccttttgtt aggtttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg 60
tttaggcagt gctagtaatt tcctcgtaat gattctgtta ttactttcct attctttatt 120
cctctttctt ctgaagatta atgaagttga aaattgaggt ggataaatac aaaaaggtag 180
tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt 240
atgcaagtta gtaattactc agggttaact aaattacttt aatatgctgt tgaacctact 300
ctgttccttg gctagaaaaa attataaaca ggactttgtt agtttgggaa gccaaattga 360
taatattcta tgttctaaaa gttgggctat acataaanta tnaagaaata tggaatttta 420
ttcccaggaa tatggggttc atttatgaat antacccggg anagaagttt tgantnaaac 480
cngttttggt taatacgtta atatgtcctn aatnaacaag gcntgactta tttccaaaaa 540
aaaaaaaaaa aa 552

<210> 80
<211> 476
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(476)
<223> n = A,T,C or G

<400> 80
acagggattt gagatgctaa ggccccagag atcgtttgat ccaaccctct tattttcaga 60
ggggaaaatg gggcctagaa gttacagagc atctagctgg tgcgctggca cccctggcct 120
cacacagact cccgagtagc tgggactaca ggcacacagt cactgaagca ggccctgttt 180
gcaattcacg ttgccacctc caacttaaac attcttcata tgtgatgtcc ttagtcacta 240
aggttaaact ttcccaccca gaaaaggcaa cttagataaa atcttagagt actttcatac 300
tcttctaagt cctcttccag cctcactttg agtcctcctt gggggttgat aggaantntc 360
tcttggcttt ctcaataaaa tctctatcca tctcatgttt aatttggtac gcntaaaaat 420
gctgaaaaaa ttaaaatgtt ctggtttcnc tttaaaaaaa aaaaaaaaaa aaaaaa 476

<210> 81
<211> 232
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(232)
<223> n = A,T,C or G

<400> 81
tttttttttg tatgccntcn ctgtggngtt attgttgctg ccaccctgga ggagcccagt 60
ttcttctgta tctttctttt ctgggggatc ttcctggctc tgcccctcca ttcccagcct 120
ctcatcccca tcttgcactt ttgctagggt tggaggcgct ttcctggtag cccctcagag 180
actcagtcag cgggaataag tcctaggggt gggggtgtg gcaagccggc ct 232

<210> 82
<211> 383
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(383)
<223> n = A,T,C or G

<400> 82
aggcgggagc agaagctaaa gccaaagccc aagaagagtg gcagtgccag cactggtgcc 60
agtaccagta ccaataacat gccagtgcca gtgccagcac cagtggtggc ttcagtgctg 120
gtgccagcct gaccgccact ctcacatttg ggctcttcgc tggccttggt ggagctggtg 180
ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtgagat tttagatatt 240
gttaatcctg ccagtctttc tcttcaagcc agggtgcatc ctcagaaacc tactcaacac 300
agcactctng gcagccacta tcaatcaatt gaagttgaca ctctgcatta aatctatttg 360
ccatttcaaa aaaaaaaaaa aaa 383

<210> 83
<211> 494
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(494)
<223> n = A,T,C or G

<400> 83
accgaattgg gaccgctggc ttataagcga tcatgtcctc cagtattacc tcaacgagca 60
gggagatcga gtctatacgc tgaagaaatt tgacccgatg ggacaacaga cctgctcagc 120
ccatcctgct cggttctccc cagatgacaa atactctcga caccgaatca ccatcaagaa 180
acgcttcaag gtgctcatga cccagcaacc gcgccctgtc ctctgagggt ccttaaactg 240
atgtcttttc tgccacctgt tacccctcgg agactccgta accaaactct tcggactgtg 300
agccctgatg cctttttgcc agccatactc tttggcntcc agtctctcgt ggcgattgat 360
tatgcttgtg tgaggcaatc atggtggcat cacccatnaa gggaacacat ttganttttt 420
tttcncatat tttaaattac naccagaata nttcagaata aatgaattga aaaactctta 480
aaaaaaaaaa aaaa 494

<210> 84
<211> 380
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(380)
<223> n = A,T,C or G

<400> 84

```
gctggtagcc tatggcgtgg ccacggangg gctcctgagg cacgggacag tgacttccca      60
agtatcctgc gccgcgtctt ctaccgtccc tacctgcaga tcttcgggca gattccccag     120
gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg     180
gcacaccctc ctggggccca ggcgggcacc tgcgtctccc agtatgccaa ctggctggtg     240
gtgctgctcc tcgtcatctt cctgctcgtg gccaacatcc tgctggtcac ttgctcattg     300
ccatgttcag ttacacattc ggcaaagtac agggcaacag cnatctctac tgggaaggcc     360
agcgttnccg cctcatccgg                                                 380

<210> 85
<211> 481
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(481)
<223> n = A,T,C or G

<400> 85
gagttagctc ctccacaacc ttgatgaggt cgtctgcagt ggcctctcgc ttcataccgc      60
tnccatcgtc atactgtagg tttgccacca cctcctgcat cttggggcgg ctaatatcca     120
ggaaactctc aatcaagtca ccgtcnatna aacctgtggc tggttctgtc ttccgctcgg     180
tgtgaaagga tctccagaag gagtgctcga tcttccccac acttttgatg actttattga     240
gtcgattctg catgtccagc aggaggttgt accagctctc tgacagtgag gtcaccagcc     300
ctatcatgcc nttgaacgtg ccgaagaaca ccgagccttg tgtggggggt gnagtctcac     360
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggnngaa     420
aaagaacacc tcctggaagt gctngccgct cctcgtccnt tggtggnngc gcntnccttt     480
t                                                                     481

<210> 86
<211> 472
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(472)
<223> n = A,T,C or G

<400> 86
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgctg agaattcatt      60
acttggaaaa gcaacttnaa gcctggacac tggtattaaa attcacaata tgcaacactt     120
taaacagtgt gtcaatctgc tcccttactt tgtcatcacc agtctgggaa taagggtatg     180
ccctattcac acctgttaaa agggcgctaa gcatttttga ttcaacatct tttttttga      240
cacaagtccg aaaaaagcaa aagtaaacag ttnttaattt gttagccaat tcactttctt     300
catgggacag agccatttga tttaaaaagc aaattgcata atattgagct ttgggagctg     360
atatntgagc ggaagantag cctttctact tcaccagaca caactccttt catattggga     420
tgttnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg             472

<210> 87
<211> 413
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(413)
<223> n = A,T,C or G
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<400> 87
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg 60
tgtgtgtgcg cgcatattat atagacaggc acatcttttt tacttttgta aaagcttatg 120
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct 180
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt 240
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc cttgactagg 300
ggggacaaag aaaagcanaa ctgaacatna gaaacaattn cctggtgaga aattncataa 360
acagaaattg ggtngtatat tgaaananng catcattnaa acgttttttt ttt 413

<210> 88
<211> 448
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(448)
<223> n = A,T,C or G

<400> 88
cgcagcgggt cctctctatc tagctccagc ctctcgcctg ccccactccc cgcgtcccgc 60
gtcctagccn accatggccg ggcccctgcg cgccccgctg ctcctgctgg ccatcctggc 120
cgtggccctg gccgtgagcc ccgcggccgg ctccagtccc ggcaagccgc cgcgcctggt 180
gggaggccca tggaccccgc gtggaagaag aaggtgtgcg gcgtgcactg gactttgccg 240
tcggcnanta caacaaaccc gcaacnactt ttaccnagcn cgcgctgcag gttgtgccgc 300
cccaancaaa ttgttactng gggtaantaa ttcttggaag ttgaacctgg gccaaacnng 360
tttaccagaa ccnagccaat tngaacaatt ncccctccat aacagcccct tttaaaaagg 420
gaancantcc tgntcttttc caaatttt 448

<210> 89
<211> 463
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(463)
<223> n = A,T,C or G

<400> 89
gaattttgtg cactggccac tgtgatggaa ccattgggcc aggatgcttt gagtttatca 60
gtagtgattc tgccaaagtt ggtgttgtaa catgagtatg taaaatgtca aaaattagc 120
agaggtctag gtctgcatat cagcagacag tttgtccgtg tattttgtag ccttgaagtt 180
ctcagtgaca agttnnttct gatgcgaagt tctnattcca gtgttttagt cctttgcatc 240
tttnatgttn agacttgcct ctntnaaatt gcttttgtnt tctgcaggta ctatctgtgg 300
tttaacaaaa tagaannact tctctgcttn gaanatttga atatcttaca tctnaaaatn 360
aattctctcc ccatannaaa acccangccc ttgggganaat ttgaaaaang gntccttcnn 420
aattcnnana anttcagntn tcatacaaca naacnggacnc ccc 463

<210> 90
<211> 400
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(400)

<223> n = A,T,C or G

<400> 90
agggattgaa ggtctnttnt actgtcggac tgttcancca ccaactctac aagttgctgt 60
cttccactca ctgtctgtaa gcntnttaac ccagactgta tcttcataaa tagaacaaat 120
tcttcaccag tcacatcttc taggaccttt ttggattcag ttagtataag ctcttccact 180
tcctttgtta agacttcatc tggtaaagtc ttaagttttg tagaaaggaa tttaattgct 240
cgttctctaa caatgtcctc tccttgaagt atttggctga acaacccacc tnaagtccct 300
ttgtgcatcc attttaaata tacttaatag ggcattggtn cactaggtta aattctgcaa 360
gagtcatctg tctgcaaaag ttgcgttagt atatctgcca 400

<210> 91
<211> 480
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(480)
<223> n = A,T,C or G

<400> 91
gagctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact 60
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac 120
atgcctcttt gactaccgtg tgccagtgct ggtgattctc acacacctcc nnccgctctt 180
tgtggaaaaa ctggcacttg nctggaacta gcaagacatc acttacaaat tcacccacga 240
gacacttgaa aggtgtaaca aagcgactct tgcattgctt tttgtccctc cggcaccagt 300
tgtcaatact aaccccgctgg tttgcctcca tcacatttgt gatctgtagc tctggataca 360
tctcctgaca gtactgaaga acttcttctt ttgtttcaaa agcaactctt ggtgcctgtt 420
ngatcaggtt cccatttccc agtccgaatg ttcacatggc atatnttact tcccacaaaa 480

<210> 92
<211> 477
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(477)
<223> n = A,T,C or G

<400> 92
atacagccca natcccacca cgaagatgcg cttgttgact gagaacctga tgcggtcact 60
ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcctt 120
cccacgcagg cagcagcggg gccggtcaat gaactccact cgtggcttgg ggttgacggt 180
taantgcagg aagaggctga ccacctcgcg gtccaccagg atgcccgact gtgcgggacc 240
tgcagcgaaa ctcctcgatg gtcatgagcg ggaagcgaat gangcccagg gccttgccca 300
gaaccttccg cctgttctct ggcgtcacct gcagctgctg ccgctnacac tcggcctcgg 360
accagcggac aaacggcgtt gaacagccgc acctcacgga tgcccantgt gtcgcgctcc 420
aggaacggcn ccagcgtgtc caggtcaatg tcggtgaanc ctccgcgggt aatggcg 477

<210> 93
<211> 377
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(377)
<223> n = A,T,C or G

<400> 93
gaacggctgg accttgcctc gcattgtgct gctggcagga ataccttggc aagcagctcc 60
agtccgagca gccccagacc gctgccgccc gaagctaagc ctgcctctgg ccttcccctc 120
cgcctcaatg cagaaccant agtgggagca ctgtgtttag agttaagagt gaacactgtn 180
tgattttact tgggaatttc ctctgttata tagcttttcc caatgctaat ttccaaacaa 240
caacaacaaa ataacatgtt tgcctgttna gttgtataaa agtangtgat tctgtatnta 300
aagaaaatat tactgttaca tatactgctt gcaanttctg tatttattgg tnctctggaa 360
ataaatatat tattaaa 377

<210> 94
<211> 495
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(495)
<223> n = A,T,C or G

<400> 94
ccctttgagg ggttagggtc cagttcccag tggaagaaac aggccaggag aantgcgtgc 60
cgagctgang cagatttccc acagtgaccc cagagccctg ggctatagtc tctgacccct 120
ccaaggaaag accaccttct ggggacatgg gctggagggc aggacctaga ggcaccaagg 180
gaaggcccca ttccggggct gttccccgag gaggaaggga aggggctctg tgtgcccccc 240
acgaggaana ggccctgant cctgggatca nacacccctt cacgtgtatc cccacacaaa 300
tgcaagctca ccaaggtccc ctctcagtcc cttccctaca ccctgaacgg ncactggccc 360
acacccaccc agancancca cccgccatgg ggaatgtnct caaggaatcg cngggcaacg 420
tggactctng tcccnnaagg gggcagaatc tccaatagan gganngaacc cttgctnana 480
aaaaaaaana aaaaa 495

<210> 95
<211> 472
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(472)
<223> n = A,T,C or G

<400> 95
ggttacttgg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc 60
cctctggaag ccttgcgcag agcggacttt gtaattgttg gagaataact gctgaatttt 120
tagctgtttt gagttgattc gcaccactgc accacaactc aatatgaaaa ctatttnact 180
tatttattat cttgtgaaaa gtatacaatg aaaattttgt tcatactgta tttatcaagt 240
atgatgaaaa gcaatagata tatattcttt tattatgttn aattatgatt gccattatta 300
atcggcaaaa tgtggagtgt atgttctttt cacagtaata tatgcctttt gtaacttcac 360
ttggttattt tattgtaaat gaattacaaa attcttaatt taagaaaatg gtangttata 420
tttanttcan taatttcttt ccttgtttac gttaattttg aaaagaatgc at 472

<210> 96
<211> 476
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(476)
<223> n = A,T,C or G

<400> 96
ctgaagcatt tcttcaaact tntctacttt tgtcattgat acctgtagta agttgacaat 60
gtggtgaaat ttcaaaatta tatgtaactt ctactagttt tactttctcc cccaagtctt 120
ttttaactca tgatttttac acacacaatc cagaacttat tatatagcct ctaagtcttt 180
attcttcaca gtagatgatg aaagagtcct ccagtgtctt gngcanaatg ttctagntat 240
agctggatac atacngtggg agttctataa actcatacct cagtgggact naaccaaaat 300
tgtgttagtc tcaattccta ccacactgag ggagcctccc aaatcactat attcttatct 360
gcaggtactc ctccagaaaa acngacaggg caggcttgca tgaaaaagtn acatctgcgt 420
tacaaagtct atcttcctca nangtctgtn aaggaacaat ttaatcttct agcttt 476

<210> 97
<211> 479
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(479)
<223> n = A,T,C or G

<400> 97
actctttcta atgctgatat gatcttgagt ataagaatgc atatgtcact agaatggata 60
aaataatgct gcaaacttaa tgttcttatg caaaatggaa cgctaatgaa acacagctta 120
caatcgcaaa tcaaaactca caagtgctca tctgttgtag atttagtgta ataagactta 180
gattgtgctc cttcggatat gattgtttct canatcttgg gcaatnttcc ttagtcaaat 240
caggctacta gaattctgtt attggatatn tgagagcatg aaatttttaa naatacactt 300
gtgattatna aattaatcac aaatttcact tatacctgct atcagcagct agaaaaacat 360
ntnnttttta natcaaagta ttttgtgttt ggaantgtnn aaatgaaatc tgaatgtggg 420
ttcnatctta ttttttcccn gacnactant tncttttttta gggnctattc tganccatc 479

<210> 98
<211> 461
<212> DNA
<213> Homo sapien

<400> 98
agtgacttgt cctccaacaa aacccccttga tcaagtttgt ggcactgaca atcagaccta 60
tgctagttcc tgtcatctat tcgctactaa atgcagactg gaggggacca aaaaggggca 120
tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga 180
agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta 240
tgaagccact ctgaacacgc tggttatcta gatgagaaca gagaaataaa gtcagaaaat 300
ttacctggag aaaagaggct ttggctgggg accatcccat tgaaccttct cttaaggact 360
ttaagaaaaa ctaccacatg ttgtgtatcc tggtgccggc cgtttatgaa ctgaccaccc 420
tttggaataa tcttgacgct cctgaacttg ctcctctgcg a 461

<210> 99
<211> 171
<212> DNA
<213> Homo sapien

<400> 99
gtggccgcgc gcaggtgttt cctcgtaccg cagggccccc tcccttcccc aggcgtccct 60
cggcgcctct gcgggcccga ggaggagcgg ctggcgggtg gggggagtgt gacccaccct 120

cggtgagaaa agccttctct agcgatctga gaggcgtgcc ttgggggtac c 171

<210> 100
<211> 269
<212> DNA
<213> Homo sapien

<400> 100
cggccgcaag tgcaactcca gctggggccg tgcggacgaa gattctgcca gcagttggtc 60
cgactgcgac gacggcggcg gcgacagtcg caggtgcagc gcgggcgcct ggggtcttgc 120
aaggctgagc tgacgccgca gaggtcgtgt cacgtcccac gaccttgacg ccgtcgggga 180
cagccggaac agagcccggt gaagcgggag gcctcgggga gcccctcggg aagggcggcc 240
cgagagatac gcaggtgcag gtggccgcc 269

<210> 101
<211> 405
<212> DNA
<213> Homo sapien

<400> 101
tttttttttt ttttggaatc tactgcgagc acagcaggtc agcaacaagt ttattttgca 60
gctagcaagg taacagggta gggcatggtt acatgttcag gtcaacttcc tttgtcgtgg 120
ttgattggtt tgtctttatg ggggcggggt ggggtagggg aaacgaagca aataacatgg 180
agtgggtgca ccctccctgt agaacctggt tacaaagctt ggggcagttc acctggtctg 240
tgaccgtcat ttcttgaca tcaatgttat tagaagtcag gatatctttt agagagtcca 300
ctgttctgga gggagattag ggtttcttgc caaatccaac aaaatccact gaaaaagttg 360
gatgatcagt acgaataccg aggcatattc tcatatcggt ggcca 405

<210> 102
<211> 470
<212> DNA
<213> Homo sapien

<400> 102
tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 60
ggcacttaat ccatttttat ttcaaaatgt ctacaaattt aatcccatta tacggtattt 120
tcaaaatcta aattattcaa attagccaaa tccttaccaa ataataccca aaaatcaaaa 180
atatacttct ttcagcaaac ttgttacata aattaaaaaa atatatacgg ctggtgtttt 240
caaagtacaa ttatcttaac actgcaaaca ttttaaggaa ctaaaataaa aaaaaacact 300
ccgcaaaggt taaagggaac aacaaattct tttacaacac cattataaaa atcatatctc 360
aaatcttagg ggaatatata cttcacacgg gatcttaact tttactcact ttgtttattt 420
ttttaaacca ttgtttgggc ccaacacaat ggaatccccc ctggactagt 470

<210> 103
<211> 581
<212> DNA
<213> Homo sapien

<400> 103
tttttttttt ttttttttga ccccccctctt ataaaaaaca agttaccatt ttattttact 60
tacacatatt tattttataa ttggtattag atattcaaaa ggcagctttt aaaatcaaac 120
taaatggaaa ctgccttaga tacataattc ttaggaatta gcttaaaatc tgcctaaagt 180
gaaaatcttc tctagctctt ttgactgtaa atttttgact cttgtaaaac atccaaattc 240
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gcttctctag cctcatttcc tagctcttat ctactattag taagtggctt ttttcctaaa 360
agggaaaaca ggaagagaaa tggcacacaa aacaaacatt ttatattcat atttctacct 420
acgttaataa aatagcattt tgtgaagcca gctcaaaaga aggcttagat ccttttatgt 480
ccattttagt cactaaacga tatcaaagtg ccagaatgca aaaggtttgt gaacatttat 540

tcaaaagcta atataagata tttcacatac tcatctttct g 581

<210> 104
<211> 578
<212> DNA
<213> Homo sapien

<400> 104
tttttttttt tttttttttt tttttctctt cttttttttt gaaatgagga tcgagttttt 60
cactctctag atagggcatg aagaaaactc atctttccag ctttaaaata acaatcaaat 120
ctcttatgct atatcatatt ttaagttaaa ctaatgagtc actggcttat cttctcctga 180
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ttcatgcaaa ctagaaaata atgtttcttt tgcataagag aagagaacaa tatagcatta 360
caaaactgct caaattgttt gttaagttat ccattataat tagttggcag gagctaatac 420
aaatcacatt tacgacagca ataataaaac tgaagtacca gttaaatatc caaaataatt 480
aaaggaacat ttttagcctg ggtataatta gctaattcac tttacaagca tttattagaa 540
tgaattcaca tgttattatt cctagcccaa cacaatgg 578

<210> 105
<211> 538
<212> DNA
<213> Homo sapien

<400> 105
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gtcttgaaca ccaatattaa tttgaggaaa atacaccaaa atacattaag taaattattt 180
aagatcatag agcttgtaag tgaaaagata aaatttgacc tcagaaactc tgagcattaa 240
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ggggtgtcac tggtaaacca acacattctg aaggatacat tacttagtga tagattctta 360
tgtactttgc taatacgtgg atatgagttg acaagtttct ctttcttcaa tcttttaagg 420
ggcgagaaat gaggaagaaa agaaaaggat tacgcatact gttctttcta tggaaggatt 480
agatatgttt cctttgccaa tattaaaaaa ataataatgt ttactactag tgaaaccc 538

<210> 106
<211> 473
<212> DNA
<213> Homo sapien

<400> 106
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atttattagc tctgcaactt acatatttaa attaaagaaa cgttttagac aactgtacaa 120
tttataaatg taaggtgcca ttattgagta atatattcct ccaagagtgg atgtgtccct 180
tctcccacca actaatgaac agcaacatta gtttaatttt attagtagat atacactgct 240
gcaaacgcta attctcttct ccatccccat gtgatattgt gtatatgtgt gagttggtag 300
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agactgtgtc tgtctgaatc aaatgatctg acctatcctc ggtggcaaga actcttcgaa 420
ccgcttcctc aaaggcgctg ccacatttgt ggctctttgc acttgtttca aaa 473

<210> 107
<211> 1621
<212> DNA
<213> Homo sapien

<400> 107
cgccatggca ctgcagggca tctcggtcat ggagctgtcc ggcctggccc cgggcccgtt 60
ctgtgctatg gtcctggctg acttcggggc gcgtgtggta cgcgtggacc ggcccggctc 120

ccgctacgac gtgagccgct tgggccgggg caagcgctcg ctagtgctgg acctgaagca 180
gccgcgggga gccgccgtgc tgcggcgtct gtgcaagcgg tcggatgtgc tgctggagcc 240
cttccgccgc ggtgtcatgg agaaactcca gctgggccca gagattctgc agcgggaaaa 300
tccaaggctt atttatgcca ggctgagtgg atttggccag tcaggaagct tctgccggtt 360
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tggtgagaat ccgtatgccc cgctgaatct cctggctgac tttgctggtg gtggccttat 480
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cattgatgca aatatggtgg aaggaacagc atatttaagt tcttttctgt ggaaaactca 600
gaaatcgagt ctgtgggaag cacctcgagg acagaacatg ttggatggtg gagcaccttt 660
ctatacgact tacaggacag cagatgggga attcatggct gttggagcaa tagaacccca 720
gttctacgag ctgctgatca aaggacttgg actaaagtct gatgaacttc ccaatcagat 780
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aatggttatc attagggctt ttgatttata aaactttggg tacttatact aaattatggt 1380
agttattctg ccttccagtt tgcttgatat atttgttgat attaagattc ttgacttata 1440
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atttacactc ttgattctac aatgtagaaa atgaggaaat gccacaaatt gtatggtgat 1560
aaaagtcacg tgaaacaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620
a 1621

<210> 108
<211> 382
<212> PRT
<213> Homo sapien

<400> 108
Met Ala Leu Gln Gly Ile Ser Val Met Glu Leu Ser Gly Leu Ala Pro
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Gly Pro Phe Cys Ala Met Val Leu Ala Asp Phe Gly Ala Arg Val Val
20 25 30
Arg Val Asp Arg Pro Gly Ser Arg Tyr Asp Val Ser Arg Leu Gly Arg
35 40 45
Gly Lys Arg Ser Leu Val Leu Asp Leu Lys Gln Pro Arg Gly Ala Ala
50 55 60
Val Leu Arg Arg Leu Cys Lys Arg Ser Asp Val Leu Leu Glu Pro Phe
65 70 75 80
Arg Arg Gly Val Met Glu Lys Leu Gln Leu Gly Pro Glu Ile Leu Gln
85 90 95
Arg Glu Asn Pro Arg Leu Ile Tyr Ala Arg Leu Ser Gly Phe Gly Gln
100 105 110
Ser Gly Ser Phe Cys Arg Leu Ala Gly His Asp Ile Asn Tyr Leu Ala
115 120 125
Leu Ser Gly Val Leu Ser Lys Ile Gly Arg Ser Gly Glu Asn Pro Tyr
130 135 140
Ala Pro Leu Asn Leu Leu Ala Asp Phe Ala Gly Gly Gly Leu Met Cys
145 150 155 160
Ala Leu Gly Ile Ile Met Ala Leu Phe Asp Arg Thr Arg Thr Asp Lys
165 170 175
Gly Gln Val Ile Asp Ala Asn Met Val Glu Gly Thr Ala Tyr Leu Ser
180 185 190
Ser Phe Leu Trp Lys Thr Gln Lys Ser Ser Leu Trp Glu Ala Pro Arg

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        195                 200                 205
Gly Gln Asn Met Leu Asp Gly Gly Ala Pro Phe Tyr Thr Thr Tyr Arg
    210                 215                 220
Thr Ala Asp Gly Glu Phe Met Ala Val Gly Ala Ile Glu Pro Gln Phe
225                 230                 235                 240
Tyr Glu Leu Leu Ile Lys Gly Leu Gly Leu Lys Ser Asp Glu Leu Pro
                245                 250                 255
Asn Gln Met Ser Met Asp Asp Trp Pro Glu Met Lys Lys Lys Phe Ala
            260                 265                 270
Asp Val Phe Ala Lys Lys Thr Lys Ala Glu Trp Cys Gln Ile Phe Asp
        275                 280                 285
Gly Thr Asp Ala Cys Val Thr Pro Val Leu Thr Phe Glu Glu Val Val
    290                 295                 300
His His Asp His Asn Lys Glu Arg Gly Ser Phe Ile Thr Ser Glu Glu
305                 310                 315                 320
Gln Asp Val Ser Pro Arg Pro Ala Pro Leu Leu Leu Asn Thr Pro Ala
                325                 330                 335
Ile Pro Ser Phe Lys Arg Asp Pro Phe Ile Gly Glu His Thr Glu Glu
            340                 345                 350
Ile Leu Glu Glu Phe Gly Phe Ser Arg Glu Glu Ile Tyr Gln Leu Asn
        355                 360                 365
Ser Asp Lys Ile Ile Glu Ser Asn Lys Val Lys Ala Ser Leu
    370                 375                 380
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<210> 109
<211> 1524
<212> DNA
<213> Homo sapien

<400> 109

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cagtgcgacc tagtggctct cacctgcttc ctcctgggcg tgggctgccg gctgaccccg   180
ggtttgtacc acctgggccg cactgtcctc tgcatcgact tcatggtttt cacggtgcgg   240
ctgcttcaca tcttcacggt caacaaacag ctggggccca agatcgtcat cgtgagcaag   300
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gtggccacgg aggggctcct gaggccacgg gacagtgact tcccaagtat cctgcgccgc   420
gtcttctacc gtccctacct gcagatcttc gggcagattc cccaggagga catggacgtg   480
gccctcatgg agcacagcaa ctgctcgtcg gagcccggct tctgggcaca ccctcctggg   540
gcccaggcgg gcacctgcgt ctcccagtat gccaactggc tggtggtgct gctcctcgtc   600
atcttcctgc tcgtggccaa catcctgctg gtcaacttgc tcattgccat gttcagttac   660
acattcggca aagtacaggg caacagcgat ctctactgga aggcgcagcg ttaccgcctc   720
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gagcgtctga agcgcacgtc ccagaaggtg gacttggcac tgaaacagct gggacacatc  1020
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ctggggtggg tggccgaggc cctgagccgc tctgccttgc tgcccccagg tgggccgcca  1140
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ccacagggga tttgctcct agagtaaggc tcatctgggc ctcggccccc gcacctggtg   1260
gccttgtcct tgaggtgagc cccatgtcca tctgggccac tgtcaggacc acctttggga  1320
gtgtcatcct tacaaaccac agcatgcccg gctcctccca gaaccagtcc cagcctggga  1380
ggatcaaggc ctggatcccg ggccgttatc catctggagg ctgcagggtc cttggggtaa  1440
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cagaggaaaa aaaaaaaaa aaaa                                          1524
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<210> 110

<211> 3410
<212> DNA
<213> Homo sapien

<400> 110
gggaaccagc ctgcacgcgc tggctccggg tgacagccgc gcgcctcggc caggatctga 60
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aagctggacc ggcaccaaag ggctggcaga aatgggcgcc tggctgattc ctaggcagtt 180
ggcggcagca aggaggagag gccgcagctt ctggagcaga gccgagacga agcagttctg 240
gagtgcctga acggccccct gagccctacc cgcctggccc actatggtcc agaggctgtg 300
ggtgagccgc ctgctgcggc accggaaagc ccagctcttg ctggtcaacc tgctaacctt 360
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ctgtgtcccg ctcctaggct cagccagtga ccactggcgt ggacgctatg gccgccgccg 540
gcccttcatc tgggcactgt ccttgggcat cctgctgagc ctctttctca tcccaagggc 600
cggctggcta gcagggctgc tgtgcccgga tcccaggccc ctggagctgg cactgctcat 660
cctgggcgtg gggctgctgg acttctgtgg ccaggtgtgc ttcactccac tggaggccct 720
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cttcctcacc tgcgtagcag ccacactgct ggtggctgag gaggcagcgc tgggccccac 960
cgagccagca gaagggctgt cggccccctc cttgtcgccc cactgctgtc catgccgggc 1020
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tttctaggat gaaacactcc tccatgggat ttgaacatat gacttatttg taggggaaga 2460
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gaggtcttat ctctcagggg gggtttaagt gccgtttgca ataatgtcgt cttatttatt 3240
tagcggggtg aatattttat actgtaagtg agcaatcaga gtataatgtt tatggtgaca 3300
aaattaaagg ctttcttata tgtttaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 3360
aaaaaaaara aaaaaaaaaa aaaaaaaaaa aaaaaaataa aaaaaaaaaa 3410

<210> 111
<211> 1289
<212> DNA
<213> Homo sapien

<400> 111
agccaggcgt ccctctgcct gcccactcag tggcaacacc cgggagctgt tttgtccttt 60
gtggagcctc agcagttccc tctttcagaa ctcactgcca agagccctga acaggagcca 120
ccatgcagtg cttcagcttc attaagacca tgatgatcct cttcaatttg ctcatctttc 180
tgtgtggtgc agccctgttg gcagtgggca tctgggtgtc aatcgatggg gcatcctttc 240
tgaagatctt cgggccactg tcgtccagtg ccatgcagtt tgtcaacgtg ggctacttcc 300
tcatcgcagc cggcgttgtg gtctttgctc ttggtttcct gggctgctat ggtgctaaga 360
ctgagagcaa gtgtgccctc gtgacgttct tcttcatcct cctcctcatc ttcattgctg 420
aggttgcagc tgctgtggtc gccttggtgt acaccacaat ggctgagcac ttcctgacgt 480
tgctggtagt gcctgccatc aagaaagatt atggttccca ggaagacttc actcaagtgt 540
ggaacaccac catgaaaggg ctcaagtgct gtggcttcac caactatacg gattttgagg 600
actcacccta cttcaaagag aacagtgcct ttccccccatt ctgttgcaat gacaacgtca 660
ccaacacagc caatgaaacc tgcaccaagc aaaaggctca cgaccaaaaa gtagagggtt 720
gcttcaatca gcttttgtat gacatccgaa ctaatgcagt caccgtgggt ggtgtggcag 780
ctggaattgg gggcctcgag ctggctgcca tgattgtgtc catgtatctg tactgcaatc 840
tacaataagt ccacttctgc ctctgccact actgctgcca catgggaact gtgaagaggc 900
accctggcaa gcagcagtga ttgggggagg ggacaggatc taacaatgtc acttgggcca 960
gaatggacct gccctttctg ctccagactt ggggctagat agggaccact ccttttagcg 1020
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gtagccagtt ctgttgccca ttcccccagt ctattaaacc cttgatatgc cccctaggcc 1140
tagtggtgat cccagtgctc tactgggggga tgagagaaag gcattttata gcctgggcat 1200
aagtgaaatc agcagagcct ctgggtggat gtgtagaagg cacttcaaaa tgcataaacc 1260
tgttacaatg ttaaaaaaaa aaaaaaaaa 1289

<210> 112
<211> 315
<212> PRT
<213> Homo sapien

<400> 112
Met Val Phe Thr Val Arg Leu Leu His Ile Phe Thr Val Asn Lys Gln
1 5 10 15
Leu Gly Pro Lys Ile Val Ile Val Ser Lys Met Met Lys Asp Val Phe
20 25 30
Phe Phe Leu Phe Phe Leu Gly Val Trp Leu Val Ala Tyr Gly Val Ala
35 40 45
Thr Glu Gly Leu Leu Arg Pro Arg Asp Ser Asp Phe Pro Ser Ile Leu
50 55 60
Arg Arg Val Phe Tyr Arg Pro Tyr Leu Gln Ile Phe Gly Gln Ile Pro
65 70 75 80
Gln Glu Asp Met Asp Val Ala Leu Met Glu His Ser Asn Cys Ser Ser
85 90 95
Glu Pro Gly Phe Trp Ala His Pro Pro Gly Ala Gln Ala Gly Thr Cys
100 105 110
Val Ser Gln Tyr Ala Asn Trp Leu Val Val Leu Leu Leu Val Ile Phe
115 120 125
Leu Leu Val Ala Asn Ile Leu Leu Val Asn Leu Leu Ile Ala Met Phe
130 135 140

Ser Tyr Thr Phe Gly Lys Val Gln Gly Asn Ser Asp Leu Tyr Trp Lys
145 150 155 160
Ala Gln Arg Tyr Arg Leu Ile Arg Glu Phe His Ser Arg Pro Ala Leu
165 170 175
Ala Pro Pro Phe Ile Val Ile Ser His Leu Arg Leu Leu Leu Arg Gln
180 185 190
Leu Cys Arg Arg Pro Arg Ser Pro Gln Pro Ser Ser Pro Ala Leu Glu
195 200 205
His Phe Arg Val Tyr Leu Ser Lys Glu Ala Glu Arg Lys Leu Leu Thr
210 215 220
Trp Glu Ser Val His Lys Glu Asn Phe Leu Leu Ala Arg Ala Arg Asp
225 230 235 240
Lys Arg Glu Ser Asp Ser Glu Arg Leu Lys Arg Thr Ser Gln Lys Val
245 250 255
Asp Leu Ala Leu Lys Gln Leu Gly His Ile Arg Glu Tyr Glu Gln Arg
260 265 270
Leu Lys Val Leu Glu Arg Glu Val Gln Gln Cys Ser Arg Val Leu Gly
275 280 285
Trp Val Ala Glu Ala Leu Ser Arg Ser Ala Leu Leu Pro Pro Gly Gly
290 295 300
Pro Pro Pro Pro Asp Leu Pro Gly Ser Lys Asp
305 310 315

<210> 113
<211> 553
<212> PRT
<213> Homo sapien

<400> 113
Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala
1 5 10 15
Gln Leu Leu Leu Val Asn Leu Leu Thr Phe Gly Leu Glu Val Cys Leu
20 25 30
Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val
35 40 45
Glu Glu Lys Phe Met Thr Met Val Leu Gly Ile Gly Pro Val Leu Gly
50 55 60
Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp Arg Gly
65 70 75 80
Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu Gly Ile
85 90 95
Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala Gly Leu
100 105 110
Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile Leu Gly
115 120 125
Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro Leu Glu
130 135 140
Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg Gln Ala
145 150 155 160
Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu Gly Tyr
165 170 175
Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu
180 185 190
Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile Phe Leu
195 200 205
Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala Leu Gly
210 215 220
Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser Pro His

```
225                 230                 235                 240
Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly Ala Leu
                245                 250                 255
Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr Leu Arg
            260                 265                 270
Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met Thr Phe
        275                 280                 285
Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln Gly Val
    290                 295                 300
Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly
305                 310                 315                 320
Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile Ser Leu
                325                 330                 335
Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg
            340                 345                 350
Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala
        355                 360                 365
Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu
    370                 375                 380
Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala
385                 390                 395                 400
Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr Arg Gly
                405                 410                 415
Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser Phe Leu
            420                 425                 430
Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val Gly Ala
        435                 440                 445
Gly Gly Ser Gly Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser
    450                 455                 460
Ala Cys Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala
465                 470                 475                 480
Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp
                485                 490                 495
Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met Gly Ser
            500                 505                 510
Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala
        515                 520                 525
Gly Leu Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val Phe Asp
    530                 535                 540
Lys Ser Asp Leu Ala Lys Tyr Ser Ala
545                 550

      <210> 114
      <211> 241
      <212> PRT
      <213> Homo sapien

      <400> 114
Met Gln Cys Phe Ser Phe Ile Lys Thr Met Met Ile Leu Phe Asn Leu
 1               5                  10                  15
Leu Ile Phe Leu Cys Gly Ala Ala Leu Leu Ala Val Gly Ile Trp Val
            20                  25                  30
Ser Ile Asp Gly Ala Ser Phe Leu Lys Ile Phe Gly Pro Leu Ser Ser
        35                  40                  45
Ser Ala Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly
    50                  55                  60
Val Val Val Phe Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr
65                  70                  75                  80
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Glu Ser Lys Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Leu Ile
                85                  90                  95
Phe Ile Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr
            100                 105                 110
Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys
        115                 120                 125
Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met
    130                 135                 140
Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp
145                 150                 155                 160
Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
                165                 170                 175
Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala
            180                 185                 190
His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile
        195                 200                 205
Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly
    210                 215                 220
Leu Glu Leu Ala Ala Met Ile Val Ser Met Tyr Leu Tyr Cys Asn Leu
225                 230                 235                 240
Gln


      <210> 115
      <211> 366
      <212> DNA
      <213> Homo sapien

      <400> 115
gctctttctc tcccctcctc tgaatttaat tctttcaact tgcaatttgc aaggattaca      60
catttcactg tgatgtatat tgtgttgcaa aaaaaaaaaa gtgtctttgt ttaaaattac     120
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga     180
actggtagaa aaacatctga agagctagtc tatcagcatc tgacaggtga attggatggt     240
tctcagaacc atttcaccca gacagcctgt ttctatcctg tttaataaat tagtttgggt     300
tctctacatg cataacaaac cctgctccaa tctgtcacat aaaagtctgt gacttgaagt     360
ttagtc                                                                366

      <210> 116
      <211> 282
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(282)
      <223> n = A,T,C or G

      <400> 116
acaaagatga accatttcct atattatagc aaaattaaaa tctacccgta ttctaatatt      60
gagaaatgag atnaaacaca atnttataaa gtctacttag agaagatcaa gtgacctcaa     120
agactttact attttcatat tttaagacac atgatttatc ctattttagt aacctggttc     180
atacgttaaa caaaggataa tgtgaacagc agagaggatt tgttggcaga aaatctatgt     240
tcaatctnga actatctana tcacagacat ttctattcct tt                        282

      <210> 117
      <211> 305
      <212> DNA
      <213> Homo sapien
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<220>
<221> misc_feature
<222> (1)...(305)
<223> n = A,T,C or G

<400> 117
acacatgtcg cttcactgcc ttcttagatg cttctggtca acatanagga acagggacca 60
tatttatcct ccctcctgaa acaattgcaa aataanacaa aatatatgaa acaattgcaa 120
aataaggcaa aatatatgaa acaacaggtc tcgagatatt ggaaatcagt caatgaagga 180
tactgatccc tgatcactgt cctaatgcag gatgtgggaa acagatgagg tcacctctgt 240
gactgcccca gcttactgcc tgtagagagt ttctangctg cagttcagac agggagaaat 300
tgggt 305

<210> 118
<211> 71
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(71)
<223> n = A,T,C or G

<400> 118
accaaggtgt ntgaatctct gacgtgggga tctctgattc ccgcacaatc tgagtggaaa 60
aantcctggg t 71

<210> 119
<211> 212
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(212)
<223> n = A,T,C or G

<400> 119
actccggttg gtgtcagcag cacgtggcat tgaacatngc aatgtggagc ccaaaccaca 60
gaaaatgggg tgaaattggc caactttcta tnaacttatg ttggcaantt tgccaccaac 120
agtaagctgg cccttctaat aaaagaaaat tgaaaggttt ctcactaanc ggaattaant 180
aatggantca aganactccc aggcctcagc gt 212

<210> 120
<211> 90
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(90)
<223> n = A,T,C or G

<400> 120
actcgttgca natcaggggc cccccagagt caccgttgca ggagtccttc tggtcttgcc 60
ctccgccggc gcagaacatg ctggggtggt 90

<210> 121
<211> 218
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(218)
<223> n = A,T,C or G

<400> 121
tgtancgtga anacgacaga nagggttgtc aaaaatggag aanccttgaa gtcattttga 60
gaataagatt tgctaaaaga tttggggcta aaacatggtt attgggagac atttctgaag 120
atatncangt aaattangga atgaattcat ggttcttttg ggaattcctt tacgatngcc 180
agcatanact tcatgtgggg atancagcta cccttgta 218

<210> 122
<211> 171
<212> DNA
<213> Homo sapien

<400> 122
taggggtgta tgcaactgta aggacaaaaa ttgagactca actggcttaa ccaataaagg 60
catttgttag ctcatggaac aggaagtcgg atggtggggc atcttcagtg ctgcatgagt 120
caccaccccg gcggggtcat ctgtgccaca ggtccctgtt gacagtgcgg t 171

<210> 123
<211> 76
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(76)
<223> n = A,T,C or G

<400> 123
tgtagcgtga agacnacaga atggtgtgtg ctgtgctatc caggaacaca tttattatca 60
ttatcaanta ttgtgt 76

<210> 124
<211> 131
<212> DNA
<213> Homo sapien

<400> 124
acctttcccc aaggccaatg tcctgtgtgc taactggccg gctgcaggac agctgcaatt 60
caatgtgctg ggtcatatgg aggggaggag actctaaaat agccaatttt attctcttgg 120
ttaagatttg t 131

<210> 125
<211> 432
<212> DNA
<213> Homo sapien

<400> 125
actttatcta ctggctatga aatagatggt ggaaaattgc gttaccaact ataccactgg 60
cttgaaaaag aggtgatagc tcttcagagg acttgtgact tttgctcaga tgctgaagaa 120

```
ctacagtctg catttggcag aaatgaagat gaatttggat taaatgagga tgctgaagat     180
ttgcctcacc aaacaaaagt gaaacaactg agagaaaatt ttcaggaaaa aagacagtgg     240
ctcttgaagt atcagtcact tttgagaatg tttcttagtt actgcatact tcatggatcc     300
catggtgggg gtcttgcatc tgtaagaatg gaattgattt tgcttttgca agaatctcag     360
caggaaacat cagaaccact attttctagc cctctgtcag agcaaacctc agtgcctctc     420
ctctttgctt gt                                                         432

      &lt;210&gt; 126
      &lt;211&gt; 112
      &lt;212&gt; DNA
      &lt;213&gt; Homo sapien

      &lt;400&gt; 126
acacaacttg aatagtaaaa tagaaactga gctgaaattt ctaattcact ttctaaccat      60
agtaagaatg atatttcccc ccagggatca ccaaatattt ataaaaattt gt             112

      &lt;210&gt; 127
      &lt;211&gt; 54
      &lt;212&gt; DNA
      &lt;213&gt; Homo sapien

      &lt;400&gt; 127
accacgaaac cacaaacaag atggaagcat caatccactt gccaagcaca gcag            54

      &lt;210&gt; 128
      &lt;211&gt; 323
      &lt;212&gt; DNA
      &lt;213&gt; Homo sapien

      &lt;400&gt; 128
acctcattag taattgtttt gttgtttcat ttttttctaa tgtctcccct ctaccagctc      60
acctgagata acagaatgaa aatggaagga cagccagatt tctcctttgc tctctgctca     120
ttctctctga agtctaggtt acccattttg gggacccatt ataggcaata aacacagttc     180
ccaaagcatt tggacagttt cttgttgtgt tttagaatgg ttttcctttt tcttagcctt     240
ttcctgcaaa aggctcactc agtcccttgc ttgctcagtg gactgggctc cccagggcct     300
aggctgcctt cttttccatg tcc                                             323

      &lt;210&gt; 129
      &lt;211&gt; 192
      &lt;212&gt; DNA
      &lt;213&gt; Homo sapien

      &lt;220&gt;
      &lt;221&gt; misc_feature
      &lt;222&gt; (1)...(192)
      &lt;223&gt; n = A,T,C or G

      &lt;400&gt; 129
acatacatgt gtgtatattt ttaaatatca cttttgtatc actctgactt tttagcatac      60
tgaaaacaca ctaacataat ttntgtgaac catgatcaga tacaacccaa atcattcatc     120
tagcacattc atctgtgata naaagatagg tgagtttcat ttccttcacg ttggccaatg     180
gataaacaaa gt                                                         192

      &lt;210&gt; 130
      &lt;211&gt; 362
      &lt;212&gt; DNA
      &lt;213&gt; Homo sapien
```

<220>
<221> misc_feature
<222> (1)...(362)
<223> n = A,T,C or G

<400> 130
ccctttttta tggaatgagt agactgtatg tttgaanatt tanccacaac ctctttgaca 60
tataatgacg caacaaaaag gtgctgttta gtcctatggt tcagtttatg cccctgacaa 120
gtttccattg tgttttgccg atcttctggc taatcgtggt atcctccatg ttattagtaa 180
ttctgtattc cattttgtta acgcctggta gatgtaacct gctangaggc taactttata 240
cttatttaaa agctcttatt ttgtggtcat taaaatggca atttatgtgc agcactttat 300
tgcagcagga agcacgtgtg ggttggttgt aaagctcttt gctaatctta aaaagtaatg 360
gg 362

<210> 131
<211> 332
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(332)
<223> n = A,T,C or G

<400> 131
ctttttgaaa gatcgtgtcc actcctgtgg acatcttgtt ttaatggagt ttcccatgca 60
gtangactgg tatggttgca gctgtccaga taaaaacatt tgaagagctc caaaatgaga 120
gttctcccag gttcgccctg ctgctccaag tctcagcagc agcctctttt aggaggcatc 180
ttctgaacta gattaaggca gcttgtaaat ctgatgtgat ttggtttatt atccaactaa 240
cttccatctg ttatcactgg agaaagccca gactccccan gacnggtacg gattgtgggc 300
atanaaggat tgggtgaagc tggcgttgtg gt 332

<210> 132
<211> 322
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(322)
<223> n = A,T,C or G

<400> 132
acttttgcca ttttgtatat ataaacaatc ttgggacatt ctcctgaaaa ctaggtgtcc 60
agtggctaag agaactcgat ttcaagcaat tctgaaagga aaaccagcat gacacagaat 120
ctcaaattcc caaacagggg ctctgtggga aaaatgaggg aggacctttg tatctcgggt 180
tttagcaagt taaaatgaan atgacaggaa aggcttattt atcaacaaag agaagagttg 240
ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct agggaagcct 300
gtaacaatct acaattggtc ca 322

<210> 133
<211> 278
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(278)

<223> n = A,T,C or G

<400> 133
acaagccttc acaagtttaa ctaaattggg attaatcttt ctgtanttat ctgcataatt 60
cttgtttttc tttccatctg gctcctgggt tgacaatttg tggaaacaac tctattgcta 120
ctatttaaaa aaaatcacaa atctttccct ttaagctatg ttnaattcaa actattcctg 180
ctattcctgt tttgtcaaag aaattatatt tttcaaaata tgtntatttg tttgatgggt 240
cccacgaaac actaataaaa accacagaga ccagcctg 278

<210> 134
<211> 121
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(121)
<223> n = A,T,C or G

<400> 134
gtttanaaaa cttgtttagc tccatagagg aaagaatgtt aaactttgta ttttaaaaca 60
tgattctctg aggttaaact tggttttcaa atgttatttt tacttgtatt ttgcttttgg 120
t 121

<210> 135
<211> 350
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(350)
<223> n = A,T,C or G

<400> 135
acttanaacc atgcctagca catcagaatc cctcaaagaa catcagtata atcctatacc 60
atancaagtg gtgactggtt aagcgtgcga caaaggtcag ctggcacatt acttgtgtgc 120
aaacttgata cttttgttct aagtaggaac tagtatacag tncctaggan tggtactcca 180
gggtgccccc caactcctgc agccgctcct ctgtgccagn ccctgnaagg aactttcgct 240
ccacctcaat caagccctgg gccatgctac ctgcaattgg ctgaacaaac gtttgctgag 300
ttcccaagga tgcaaagcct ggtgctcaac tcctggggcg tcaactcagt 350

<210> 136
<211> 399
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(399)
<223> n = A,T,C or G

<400> 136
tgtaccgtga agacgacaga agttgcatgg cagggacagg gcagggccga ggccagggtt 60
gctgtgattg tatccgaata ntcctcgtga gaaaagataa tgagatgacg tgagcagcct 120
gcagacttgt gtctgccttc aanaagccag acaggaaggc cctgcctgcc ttggctctga 180
cctggcggcc agccagccag ccacaggtgg gcttcttcct tttgtggtga caacnccaag 240
aaaactgcag aggcccaggg tcaggtgtna gtgggtangt gaccataaaa caccaggtgc 300

tcccaggaac ccgggcaaag gccatcccca cctacagcca gcatgcccac tggcgtgatg 360
ggtgcagang gatgaagcag ccagntgttc tgctgtggt 399

<210> 137
<211> 165
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(165)
<223> n = A,T,C or G

<400> 137
actggtgtgg tngggggtga tgctggtggt anaagttgan gtgacttcan gatggtgtgt 60
ggaggaagtg tgtgaacgta gggatgtaga ngttttggcc gtgctaaatg agcttcggga 120
ttggctggtc ccactggtgg tcactgtcat tggtggggtt cctgt 165

<210> 138
<211> 338
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(338)
<223> n = A,T,C or G

<400> 138
actcactgga atgccacatt cacaacagaa tcagaggtct gtgaaaacat taatggctcc 60
ttaacttctc cagtaagaat cagggacttg aaatggaaac gttaacagcc acatgcccaa 120
tgctgggcag tctcccatgc cttccacagt gaaagggctt gagaaaaatc acatccaatg 180
tcatgtgttt ccagccacac caaaaggtgc ttggggtgga gggctggggg catananggt 240
cangcctcag gaagcctcaa gttccattca gctttgccac tgtacattcc ccatntttaa 300
aaaaactgat gccttttttt tttttttttg taaaattc 338

<210> 139
<211> 382
<212> DNA
<213> Homo sapien

<400> 139
gggaatcttg gtttttggca tctggtttgc ctatagccga ggccactttg acagaacaaa 60
gaaagggact tcgagtaaga aggtgattta cagccagcct agtgcccgaa gtgaaggaga 120
attcaaacag acctcgtcat tcctggtgtg agcctggtcg gctcaccgcc tatcatctgc 180
atttgcctta ctcaggtgct accggactct ggcccctgat gtctgtagtt tcacaggatg 240
ccttatttgt cttctacacc ccacagggcc ccctacttct tcggatgtgt ttttaataat 300
gtcagctatg tgccccatcc tccttcatgc cctccctccc tttcctacca ctgctgagtg 360
gcctggaact tgtttaaagt gt 382

<210> 140
<211> 200
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(200)

<223> n = A,T,C or G

<400> 140
accaaanctt ctttctgttg tgttngattt tactataggg gtttngcttn ttctaaanat 60
acttttcatt taacancttt tgttaagtgt caggctgcac tttgctccat anaattattg 120
ttttcacatt tcaacttgta tgtgtttgtc tcttanagca ttggtgaaat cacatatttt 180
atattcagca taaaggagaa 200

<210> 141
<211> 335
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(335)
<223> n = A,T,C or G

<400> 141
actttatttt caaaacactc atatgttgca aaaaacacat agaaaaataa agtttggtgg 60
gggtgctgac taaacttcaa gtcacagact tttatgtgac agattggagc agggtttgtt 120
atgcatgtag agaacccaaa ctaatttatt aaacaggata gaaacaggct gtctgggtga 180
aatggttctg agaaccatcc aattcacctg tcagatgctg atanactagc tcttcagatg 240
tttttctacc agttcagaga tnggttaatg actanttcca atggggaaaa agcaagatgg 300
attcacaaac caagtaattt taaacaaaga cactt 335

<210> 142
<211> 459
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(459)
<223> n = A,T,C or G

<400> 142
accaggttaa tattgccaca tatatccttt ccaattgcgg gctaaacaga cgtgtattta 60
gggttgttta aagacaaccc agcttaatat caagagaaat tgtgaccttt catggagtat 120
ctgatggaga aaacactgag ttttgacaaa tcttatttta ttcagatagc agtctgatca 180
cacatggtcc aacaacactc aaataataaa tcaaatatna tcagatgtta aagattggtc 240
ttcaaacatc atagccaatg atgccccgct tgcctataat ctctccgaca taaaaccaca 300
tcaacacctc agtggccacc aaaccattca gcacagcttc cttaactgtg agctgtttga 360
agctaccagt ctgagcacta ttgactatnt ttttcangct ctgaatagct ctagggatct 420
cagcangggt gggaggaacc agctcaacct tggcgtant 459

<210> 143
<211> 140
<212> DNA
<213> Homo sapien

<400> 143
acatttcctt ccaccaagtc aggactcctg gcttctgtgg gagttcttat cacctgaggg 60
aaatccaaac agtctctcct agaaaggaat agtgtcacca accccaccca tctccctgag 120
accatccgac ttccctgtgt 140

<210> 144
<211> 164

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(164)
<223> n = A,T,C or G

<400> 144
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acttcagtaa caacatacaa taacaacatt aagtgtatat tgccatcttt gtcattttct      60
atctatacca ctctcccttc tgaaaacaan aatcactanc caatcactta tacaaatttg     120
aggcaattaa tccatatttg ttttcaataa ggaaaaaaag atgt                      164
```

<210> 145
<211> 303
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(303)
<223> n = A,T,C or G

<400> 145
```
acgtagacca tccaactttg tatttgtaat ggcaaacatc cagnagcaat tcctaaacaa      60
actggagggt atttataccc aattatccca ttcattaaca tgccctcctc ctcaggctat     120
gcaggacagc tatcataagt cggcccaggc atccagatac taccatttgt ataaacttca     180
gtaggggagt ccatccaagt gacaggtcta atcaaaggag gaaatggaac ataagcccag     240
tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccgtgg tgattaccat     300
caa                                                                   303
```

<210> 146
<211> 327
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(327)
<223> n = A,T,C or G

<400> 146
```
actgcagctc aattagaagt ggtctctgac tttcatcanc ttctccctgg gctccatgac      60
actggcctgg agtgactcat tgctctggtt ggttgagaga gctcctttgc caacaggcct     120
ccaagtcagg gctgggattt gtttcctttc cacattctag caacaatatg ctggccactt     180
cctgaacagg gagggtggga ggagccagca tggaacaagc tgccactttc taaagtagcc     240
agacttgccc ctgggcctgt cacacctact gatgaccttc tgtgcctgca ggatggaatg     300
taggggtgag ctgtgtgact ctatggt                                         327
```

<210> 147
<211> 173
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(173)
<223> n = A,T,C or G

<400> 147
acattgtttt tttgagataa agcattgana gagctctcct taacgtgaca caatggaagg 60
actggaacac atacccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt 120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gtt 173

<210> 148
<211> 477
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(477)
<223> n = A,T,C or G

<400> 148
acaaccactt tatctcatcg aatttttaac ccaaactcac tcactgtgcc tttctatcct 60
atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcatact 120
gccctactac ctgctgcaat aatcacattc ccttcctgtc ctgaccctga agccattggg 180
gtggtcctag tggccatcag tccangcctg caccttgagc ccttgagctc cattgctcac 240
nccancccac ctcaccgacc ccatcctctt acacagctac ctccttgctc tctaacccca 300
tagattatnt ccaaattcag tcaattaagt tactattaac actctacccg acatgtccag 360
caccactggt aagccttctc cagccaacac acacacacac acacncacac acacacatat 420
ccaggcacag gctacctcat cttcacaatc accccttttaa ttaccatgct atggtgg 477

<210> 149
<211> 207
<212> DNA
<213> Homo sapien

<400> 149
acagttgtat tataatatca agaaataaac ttgcaatgag agcatttaag agggaagaac 60
taacgtattt tagagagcca aggaaggttt ctgtggggag tgggatgtaa ggtggggcct 120
gatgataaat aagagtcagc caggtaagtg ggtggtgtgg tatgggcaca gtgaagaaca 180
tttcaggcag agggaacagc agtgaaa 207

<210> 150
<211> 111
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(111)
<223> n = A,T,C or G

<400> 150
accttgattt cattgctgct ctgatggaaa cccaactatc taatttagct aaaacatggg 60
cacttaaatg tggtcagtgt ttggacttgt taactantgg catctttggg t 111

<210> 151
<211> 196
<212> DNA
<213> Homo sapien

<400> 151
agcgcggcag gtcatattga acattccaga tacctatcat tactcgatgc tgttgataac 60

```
agcaagatgg ctttgaactc agggtcacca ccagctattg gaccttacta tgaaaaccat     120
ggataccaac cggaaaaccc ctatcccgca cagcccactg tggtccccac tgtctacgag     180
gtgcatccgg ctcagt                                                      196

      <210> 152
      <211> 132
      <212> DNA
      <213> Homo sapien

      <400> 152
acagcacttt cacatgtaag aagggagaaa ttcctaaatg taggagaaag ataacagaac      60
cttccccttt tcatctagtg gtggaaacct gatgctttat gttgacagga atagaaccag     120
gagggagttt gt                                                          132

      <210> 153
      <211> 285
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(285)
      <223> n = A,T,C or G

      <400> 153
acaanaccca nganaggcca ctggccgtgg tgtcatggcc tccaaacatg aaagtgtcag      60
cttctgctct tatgtcctca tctgacaact ctttaccatt tttatcctcg ctcagcagga     120
gcacatcaat aaagtccaaa gtcttggact tggccttggc ttggaggaag tcatcaacac     180
cctggctagt gagggtgcgg cgccgctcct ggatgacggc atctgtgaag tcgtgcacca     240
gtctgcaggc cctgtggaag cgccgtccac acggagtnag gaatt                     285

      <210> 154
      <211> 333
      <212> DNA
      <213> Homo sapien

      <400> 154
accacagtcc tgttgggcca gggcttcatg accctttctg tgaaaagcca tattatcacc      60
accccaaatt tttccttaaa tatctttaac tgaaggggtc agcctcttga ctgcaaagac     120
cctaagccgg ttacacagct aactcccact ggccctgatt tgtgaaattg ctgctgcctg     180
attggcacag gagtcgaagg tgttcagctc ccctcctccg tggaacgaga ctctgatttg     240
agtttcacaa attctcgggc cacctcgtca ttgctcctct gaaataaaat ccggagaatg     300
gtcaggcctg tctcatccat atggatcttc cgg                                  333

      <210> 155
      <211> 308
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(308)
      <223> n = A,T,C or G

      <400> 155
actggaaata ataaaaccca catcacagtg ttgtgtcaaa gatcatcagg gcatggatgg      60
gaaagtgctt tgggaactgt aaagtgccta acacatgatc gatgattttt gttataatat     120
ttgaatcacg gtgcatacaa actctcctgc ctgctcctcc tgggccccag ccccagcccc     180
```

atcacagctc actgctctgt tcatccaggc ccagcatgta gtggctgatt cttcttggct 240
gcttttagcc tccanaagtt tctctgaagc caaccaaacc tctangtgta aggcatgctg 300
gccctggt 308

<210> 156
<211> 295
<212> DNA
<213> Homo sapien

<400> 156
accttgctcg gtgcttggaa catattagga actcaaaata tgagatgata acagtgccta 60
ttattgatta ctgagagaac tgttagacat ttagttgaag atttctaca caggaactga 120
gaataggaga ttatgtttgg ccctcatatt ctctcctatc ctccttgcct cattctatgt 180
ctaatatatt ctcaatcaaa taaggttagc ataatcagga aatcgaccaa ataccaatat 240
aaaaccagat gtctatcctt aagattttca aatagaaaac aaattaacag actat 295

<210> 157
<211> 126
<212> DNA
<213> Homo sapien

<400> 157
acaagtttaa atagtgctgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct 60
gaagagcaaa acaaattctg tcatgtaatc tctatcttgg gtcgtgggta tatctgtccc 120
cttagt 126

<210> 158
<211> 442
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(442)
<223> n = A,T,C or G

<400> 158
acccactggt cttggaaaca cccatcctta atacgatgat ttttctgtcg tgtgaaaatg 60
aanccagcag gctgccccta gtcagtcctt ccttccagag aaaaagagat ttgagaaagt 120
gcctgggtaa ttcaccatta atttcctccc ccaaactctc tgagtcttcc cttaatattt 180
ctggtggttc tgaccaaagc aggtcatggt ttgttgagca tttgggatcc cagtgaagta 240
natgtttgta gccttgcata cttagccctt cccacgcaca aacggagtgg cagagtggtg 300
ccaaccctgt tttcccagtc cacgtagaca gattcacagt gcggaattct ggaagctgga 360
nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg 420
tgttcattct ctgatgtcct gt 442

<210> 159
<211> 498
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(498)
<223> n = A,T,C or G

<400> 159
acttccaggt aacgttgttg tttccgttga gcctgaactg atgggtgacg ttgtaggttc 60

```
tccaacaaga actgaggttg cagagcgggt agggaagagt gctgttccag ttgcacctgg     120
gctgctgtgg actgttgttg attcctcact acggcccaag gttgtggaac tggcanaaag     180
gtgtgttgtt gganttgagc tcgggcggct gtggtaggtt gtgggctctt caacaggggc     240
tgctgtggtg ccgggangtg aangtgttgt gtcacttgag cttggccagc tctggaaagt     300
antanattct tcctgaaggc cagcgcttgt ggagctggca ngggtcantg ttgtgtgtaa     360
cgaaccagtg ctgctgtggg tgggtgtana tcctccacaa agcctgaagt tatggtgtcn     420
tcaggtaana atgtggtttc agtgtccctg ggcngctgtg gaaggttgta nattgtcacc     480
aagggaataa gctgtggt                                                   498
```

<210> 160
<211> 380
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(380)
<223> n = A,T,C or G

<400> 160

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acctgcatcc agcttccctg ccaaactcac aaggagacat caacctctag acagggaaac      60
agcttcagga tacttccagg agacagagcc accagcagca aaacaaatat tcccatgcct     120
ggagcatggc atagaggaag ctganaaatg tggggtctga ggaagccatt tgagtctggc     180
cactagacat ctcatcagcc acttgtgtga agagatgccc catgacccca gatgcctctc     240
ccacccttac ctccatctca cacacttgag ctttccactc tgtataattc taacatcctg     300
gagaaaaatg gcagtttgac cgaacctgtt cacaacggta gaggctgatt tctaacgaaa     360
cttgtagaat gaagcctgga                                                 380
```

<210> 161
<211> 114
<212> DNA
<213> Homo sapien

<400> 161

```
actccacatc ccctctgagc aggcggttgt cgttcaaggt gtatttggcc ttgcctgtca      60
cactgtccac tggcccctta tccacttggt gcttaatccc tcgaaagagc atgt           114
```

<210> 162
<211> 177
<212> DNA
<213> Homo sapien

<400> 162

```
actttctgaa tcgaatcaaa tgatacttag tgtagtttta atatcctcat atatatcaaa      60
gttttactac tctgataatt ttgtaaacca ggtaaccaga acatccagtc atacagcttt     120
tggtgatata taacttggca ataacccagt ctggtgatac ataaaactac tcactgt        177
```

<210> 163
<211> 137
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(137)
<223> n = A,T,C or G

<400> 163

```
catttataca gacaggcgtg aagacattca cgacaaaaac gcgaaattct atcccgtgac      60
canagaaggc agctacggct actcctacat cctggcgtgg gtggccttcg cctgcacctt     120
catcagcggc atgatgt                                                    137

      <210> 164
      <211> 469
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(469)
      <223> n = A,T,C or G

      <400> 164
cttatcacaa tgaatgttct cctgggcagc gttgtgatct ttgccacctt cgtgacttta      60
tgcaatgcat catgctattt catacctaat gagggagttc caggagattc aaccaggaaa     120
tgcatggatc tcaaaggaaa caaacaccca ataaactcgg agtggcagac tgacaactgt     180
gagacatgca cttgctacga aacagaaatt tcatgttgca cccttgtttc tacacctgtg     240
ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg     300
gtggagaaga aggacccaaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct     360
tctagtaggc acagggctcc caggccaggc ctcattctcc tctggcctct aatagtcaat     420
gattgtgtag ccatgcctat cagtaaaaag atntttgagc aaacacttt                469

      <210> 165
      <211> 195
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(195)
      <223> n = A,T,C or G

      <400> 165
acagtttttt atanatatcg acattgccgg cacttgtgtt cagtttcata aagctggtgg      60
atccgctgtc atccactatt ccttggctag agtaaaaatt attcttatag cccatgtccc     120
tgcaggccgc ccgcccgtag ttctcgttcc agtcgtcttg gcacacaggg tgccaggact     180
tcctctgaga tgagt                                                      195

      <210> 166
      <211> 383
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(383)
      <223> n = A,T,C or G

      <400> 166
acatcttagt agtgtggcac atcagggggc catcagggtc acagtcactc atagcctcgc      60
cgaggtcgga gtccacacca ccggtgtagg tgtgctcaat cttgggcttg gcgcccacct     120
ttggagaagg gatatgctgc acacacatgt ccacaaagcc tgtgaactcg ccaaagaatt     180
tttgcagacc agcctgagca aggggcggat gttcagcttc agctcctcct tcgtcaggtg     240
gatgccaacc tcgtctangg tccgtgggaa gctggtgtcc acntcaccta caacctgggc     300
gangatctta taaagaggct ccnagataaa ctccacgaaa cttctctggg agctgctagt     360
nggggccttt ttggtgaact ttc                                             383
```

<210> 167
<211> 247
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(247)
<223> n = A,T,C or G

<400> 167
acagagccag accttggcca taaatgaanc agagattaag actaaacccc aagtcganat 60
tggagcagaa actggagcaa gaagtgggcc tggggctgaa gtagagacca aggccactgc 120
tatanccata cacagagcca actctcaggc caaggcnatg gttggggcag anccagagac 180
tcaatctgan tccaaagtgg tggctggaac actggtcatg acanaggcag tgactctgac 240
tgangtc 247

<210> 168
<211> 273
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(273)
<223> n = A,T,C or G

<400> 168
acttctaagt tttctagaag tggaaggatt gtantcatcc tgaaaatggg tttacttcaa 60
aatccctcan ccttgttctt cacnactgtc tatactgana gtgtcatgtt tccacaaagg 120
gctgacacct gagcctgnat tttcactcat ccctgagaag ccctttccag tagggtgggc 180
aattcccaac ttccttgcca caagcttccc aggctttctc ccctggaaaa ctccagcttg 240
agtcccagat acactcatgg gctgccctgg gca 273

<210> 169
<211> 431
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(431)
<223> n = A,T,C or G

<400> 169
acagccttgg cttccccaaa ctccacagtc tcagtgcaga aagatcatct tccagcagtc 60
agctcagacc agggtcaaag gatgtgacat caacagtttc tggtttcaga acaggttcta 120
ctactgtcaa atgacccccc atacttcctc aaaggctgtg gtaagttttg cacaggtgag 180
ggcagcagaa agggggtant tactgatgga caccatcttc tctgtatact ccacactgac 240
cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcactgctgg gcaccagctc 300
acgcacatca ctgacaaccg ggatggaaaa agaantgcca actttcatac atccaactgg 360
aaagtgatct gatactggat tcttaattac cttcaaaagc ttctgggggc catcagctgc 420
tcgaacactg a 431

<210> 170
<211> 266
<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(266)
<223> n = A,T,C or G

<400> 170
```
acctgtgggc tgggctgtta tgcctgtgcc ggctgctgaa agggagttca gaggtggagc     60
tcaaggagct ctgcaggcat tttgccaanc ctctccanag canagggagc aacctacact    120
ccccgctaga aagacaccag attggagtcc tgggaggggg agttggggtg ggcatttgat    180
gtatacttgt cacctgaatg aangagccag agaggaanga gacgaanatg anattggcct    240
tcaaagctag gggtctggca ggtgga                                         266
```

<210> 171
<211> 1248
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1248)
<223> n = A,T,C or G

<400> 171
```
ggcagccaaa tcataaacgg cgaggactgc agcccgcact cgcagccctg gcaggcggca     60
ctggtcatgg aaaacgaatt gttctgctcg ggcgtcctgg tgcatccgca gtgggtgctg    120
tcagccgcac actgtttcca gaagtgagtg cagagctcct acaccatcgg gctgggcctg    180
cacagtcttg aggccgacca agagccaggg agccagatgg tggaggccag cctctccgta    240
cggcacccag agtacaacag acccttgctc gctaacgacc tcatgctcat caagttggac    300
gaatccgtgt ccgagtctga caccatccgg agcatcagca ttgcttcgca gtgccctacc    360
gcggggaact cttgcctcgt ttctggctgg ggtctgctgg cgaacggcag aatgcctacc    420
gtgctgcagt gcgtgaacgt gtcggtggtg tctgaggagg tctgcagtaa gctctatgac    480
ccgctgtacc accccagcat gttctgcgcc ggcggagggc aagaccagaa ggactcctgc    540
aacggtgact ctgggggggcc cctgatctgc aacgggtact tgcagggcct tgtgtctttc    600
ggaaaagccc cgtgtggcca agttggcgtg ccaggtgtct acaccaacct ctgcaaattc    660
actgagtgga tagagaaaac cgtccaggcc agttaactct ggggactggg aacccatgaa    720
attgaccccc aaatacatcc tgcggaagga attcaggaat atctgttccc agcccctcct    780
ccctcaggcc caggagtcca ggcccccagc ccctcctccc tcaaaccaag ggtacagatc    840
cccagcccct cctccctcag acccaggagt ccagaccccc cagcccctcc tccctcagac    900
ccaggagtcc agcccctcct ccctcagacc caggagtcca gacccccccag cccctcctcc    960
ctcagaccca ggggtccagg cccccaaccc ctcctccctc agactcagag gtccaagccc   1020
ccaacccntc attccccaga cccagaggtc caggtcccag cccctcntcc ctcagaccca   1080
gcggtccaat gccacctaga ctntccctgt acacagtgcc cccttgtggc acgttgaccc   1140
aaccttacca gttggttttt cattttttngt ccctttcccc tagatccaga aataaagttt   1200
aagagaagng caaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa                 1248
```

<210> 172
<211> 159
<212> PRT
<213> Homo sapien

<220>
<221> VARIANT
<222> (1)...(159)
<223> Xaa = Any Amino Acid

<400> 172

Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro
1 5 10 15
Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser
20 25 30
Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr
35 40 45
Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly
50 55 60
Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu
65 70 75 80
Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe
85 90 95
Cys Ala Gly Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser
100 105 110
Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe
115 120 125
Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn
130 135 140
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
145 150 155

<210> 173
<211> 1265
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1265)
<223> n = A,T,C or G

<400> 173
ggcagcccgc actcgcagcc ctggcaggcg gcactggtca tggaaaacga attgttctgc 60
tcgggcgtcc tggtgcatcc gcagtgggtg ctgtcagccg cacactgttt ccagaactcc 120
tacaccatcg ggctgggcct gcacagtctt gaggccgacc aagagccagg gagccagatg 180
gtggaggcca gcctctccgt acggcaccca gagtacaaca gacccttgct cgctaacgac 240
ctcatgctca tcaagttgga cgaatccgtg tccgagtctg acaccatccg gagcatcagc 300
attgcttcgc agtgccctac cgcggggaac tcttgcctcg tttctggctg ggggtctgctg 360
gcgaacggtg agctcacggg tgtgtgtctg ccctcttcaa ggaggtcctc tgcccagtcg 420
cgggggctga cccagagctc tgcgtcccag gcagaatgcc taccgtgctg cagtgcgtga 480
acgtgtcggt ggtgtctgag gaggtctgca gtaagctcta tgacccgctg taccacccca 540
gcatgttctg cgccggcgga gggcaagacc agaaggactc ctgcaacggt gactctgggg 600
ggcccctgat ctgcaacggg tacttgcagg gccttgtgtc tttcggaaaa gccccgtgtg 660
gccaagttgg cgtgccaggt gtctacacca acctctgcaa attcactgag tggatagaga 720
aaaccgtcca ggccagttaa ctctggggac tgggaaccca tgaaattgac cccaaatac 780
atcctgcgga aggaattcag gaatatctgt tcccagcccc tcctccctca ggcccaggag 840
tccaggcccc cagcccctcc tccctcaaac caagggtaca gatccccagc ccctcctccc 900
tcagacccag gagtccagac cccccagccc ctcctccctc agacccagga gtccagcccc 960
tcctccntca gacccaggag tccagacccc ccagcccctc ctccctcaga cccaggggtt 1020
gaggccccca acccctcctc cttcagagtc agaggtccaa gcccccaacc cctcgttccc 1080
cagacccaga ggtnnaggtc ccagcccctc ttccntcaga cccagnggtc caatgccacc 1140
tagattttcc ctgnacacag tgcccccttg tggnangttg acccaacctt accagttggt 1200
ttttcatttt tngtcccttt cccctagatc cagaaataaa gtttaagaga ngngcaaaaa 1260
aaaaa 1265

<210> 174
<211> 1459
<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1459)
<223> n = A,T,C or G

<400> 174
ggtcagccgc acactgtttc cagaagtgag tgcagagctc ctacaccatc gggctgggcc 60
tgcacagtct tgaggccgac caagagccag ggagccagat ggtggaggcc agcctctccg 120
tacggcaccc agagtacaac agacccttgc tcgctaacga cctcatgctc atcaagttgg 180
acgaatccgt gtccgagtct gacaccatcc ggagcatcag cattgcttcg cagtgcccta 240
ccgcggggaa ctcttgcctc gtttctggct ggggtctgct ggcgaacggt gagctcacgg 300
gtgtgtgtct gccctcttca aggaggtcct ctgcccagtc gcgggggctg acccagagct 360
ctgcgtccca ggcagaatgc ctaccgtgct gcagtgcgtg aacgtgtcgg tggtgtctga 420
ngaggtctgc antaagctct atgacccgct gtaccacccc ancatgttct gcgccggcgg 480
agggcaagac cagaaggact cctgcaacgt gagagagggg aaaggggagg gcaggcgact 540
cagggaaggg tggagaaggg ggagacagag acacacaggg ccgcatggcg agatgcagag 600
atggagagac acacagggag acagtgacaa ctagagagag aaactgagag aaacagagaa 660
ataaacacag gaataaagag aagcaaagga agagagaaac agaaacagac atggggaggc 720
agaaacacac acacatagaa atgcagttga ccttccaaca gcatggggcc tgagggcggt 780
gacctccacc caatagaaaa tcctcttata acttttgact ccccaaaaac ctgactagaa 840
atagcctact gttgacgggg agccttacca ataacataaa tagtcgattt atgcatacgt 900
tttatgcatt catgatatac ctttgttgga atttttgat atttctaagc tacacagttc 960
gtctgtgaat ttttttaaat tgttgcaact ctcctaaaat ttttctgatg tgtttattga 1020
aaaaatccaa gtataagtgg acttgtgcat tcaaaccagg gttgttcaag ggtcaactgt 1080
gtacccagag ggaaacagtg acacagattc atagaggtga aacacgaaga gaaacaggaa 1140
aaatcaagac tctacaaaga ggctgggcag ggtggctcat gcctgtaatc ccagcacttt 1200
gggaggcgag gcaggcagat cacttgaggt aaggagttca agaccagcct ggccaaaatg 1260
gtgaaatcct gtctgtacta aaaatacaaa agttagctgg atatggtggc aggcgcctgt 1320
aatcccagct acttgggagg ctgaggcagg agaattgctt gaatatggga ggcagaggtt 1380
gaagtgagtt gagatcacac cactatactc cagctggggc aacagagtaa gactctgtct 1440
caaaaaaaaa aaaaaaaaa 1459

<210> 175
<211> 1167
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1167)
<223> n = A,T,C or G

<400> 175
gcgcagccct ggcaggcggc actggtcatg gaaaacgaat tgttctgctc gggcgtcctg 60
gtgcatccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggg 120
ctgggcctgc acagtcttga ggccgaccaa gagccaggga gccagatggt ggaggccagc 180
ctctccgtac ggcacccaga gtacaacaga ctcttgctcg ctaacgacct catgctcatc 240
aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag 300
tgccctaccg cggggaactc ttgcctcgtn tctggctggg gtctgctggc gaacggcaga 360
atgcctaccg tgctgcactg cgtgaacgtg tcggtggtgt ctgaggangt ctgcagtaag 420
ctctatgacc cgctgtacca ccccagcatg ttctgcgccg gcggagggca agaccagaag 480
gactcctgca acggtgactc tgggggcccc ctgatctgca acgggtactt gcagggcctt 540
gtgtctttcg gaaaagcccc gtgtggccaa cttggcgtgc caggtgtcta caccaacctc 600
tgcaaattca ctgagtggat agagaaaacc gtccagncca gttaactctg gggactggga 660
acccatgaaa ttgaccccca aatacatcct gcggaangaa ttcaggaata tctgttccca 720
gcccctcctc cctcaggccc aggagtccag gcccccagcc cctcctccct caaaccaagg 780

```
gtacagatcc ccagcccctc ctccctcaga cccaggagtc cagaccccc agcccctcnt      840
ccntcagacc caggagtcca gcccctcctc cntcagacgc aggagtccag accccccagc     900
ccntcntccg tcagacccag gggtgcaggc ccccaacccc tcntccntca gagtcagagg     960
tccaagcccc caacccctcg ttccccagac ccagaggtnc aggtcccagc ccctcctccc    1020
tcagacccag cggtccaatg ccacctagan tntccctgta cacagtgccc ccttgtggca    1080
ngttgaccca accttaccag ttggtttttc atttttgtc cctttcccct agatccagaa    1140
ataaagtnta agagaagcgc aaaaaaa                                        1167
```

<210> 176
<211> 205
<212> PRT
<213> Homo sapien

<220>
<221> VARIANT
<222> (1)...(205)
<223> Xaa = Any Amino Acid

<400> 176

```
Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
 1              5                  10                  15
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
            20                  25                  30
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
        35                  40                  45
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Leu Leu Leu
    50                  55                  60
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
65                  70                  75                  80
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
                85                  90                  95
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met
            100                 105                 110
Pro Thr Val Leu His Cys Val Asn Val Ser Val Val Ser Glu Xaa Val
        115                 120                 125
Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala
    130                 135                 140
Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly
145                 150                 155                 160
Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys
                165                 170                 175
Ala Pro Cys Gly Gln Leu Gly Val Pro Gly Val Tyr Thr Asn Leu Cys
            180                 185                 190
Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Xaa Ser
        195                 200                 205
```

<210> 177
<211> 1119
<212> DNA
<213> Homo sapien

<400> 177

```
gcgcactcgc agccctggca ggcggcactg gtcatggaaa acgaattgtt ctgctcgggc      60
gtcctggtgc atccgcagtg ggtgctgtca gccgcacact gtttccagaa ctcctacacc     120
atcgggctgg gcctgcacag tcttgaggcc gaccaagagc cagggagcca gatggtggag     180
gccagcctct ccgtacggca cccagagtac aacagaccct tgctcgctaa cgacctcatg     240
ctcatcaagt tggacgaatc cgtgtccgag tctgacacca tccggagcat cagcattgct     300
tcgcagtgcc ctaccgcggg gaactcttgc ctcgtttctg gctggggtct gctggcgaac     360
```

```
gatgctgtga ttgccatcca gtcccagact gtgggaggct gggagtgtga gaagctttcc      420
caaccctggc agggttgtac catttcggca acttccagtg caaggacgtc ctgctgcatc      480
ctcactgggt gctcactact gctcactgca tcacccggaa cactgtgatc aactagccag      540
caccatagtt ctccgaagtc agactatcat gattactgtg ttgactgtgc tgtctattgt      600
actaaccatg ccgatgttta ggtgaaatta gcgtcacttg gcctcaacca tcttggtatc      660
cagttatcct cactgaattg agatttcctg cttcagtgtc agccattccc acataatttc      720
tgacctacag aggtgaggga tcatatagct cttcaaggat gctggtactc ccctcacaaa      780
ttcatttctc ctgttgtagt gaaaggtgcg ccctctggag cctcccaggg tgggtgtgca      840
ggtcacaatg atgaatgtat gatcgtgttc ccattaccca aagcctttaa atccctcatg      900
ctcagtacac cagggcaggt ctagcatttc ttcatttagt gtatgctgtc cattcatgca      960
accacctcag gactcctgga ttctctgcct agttgagctc ctgcatgctg cctccttggg     1020
gaggtgaggg agagggccca tggttcaatg ggatctgtgc agttgtaaca cattaggtgc     1080
ttaataaaca gaagctgtga tgttaaaaaa aaaaaaaaa                            1119
```

<210> 178
<211> 164
<212> PRT
<213> Homo sapien

<220>
<221> VARIANT
<222> (1)...(164)
<223> Xaa = Any Amino Acid

<400> 178

```
Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
 1               5                  10                  15
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
            20                  25                  30
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
        35                  40                  45
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu
    50                  55                  60
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
65                  70                  75                  80
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
                85                  90                  95
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Asp Ala Val
            100                 105                 110
Ile Ala Ile Gln Ser Xaa Thr Val Gly Gly Trp Glu Cys Glu Lys Leu
        115                 120                 125
Ser Gln Pro Trp Gln Gly Cys Thr Ile Ser Ala Thr Ser Ser Ala Arg
    130                 135                 140
Thr Ser Cys Cys Ile Leu Thr Gly Cys Ser Leu Leu Leu Thr Ala Ser
145                 150                 155                 160
Pro Gly Thr Leu
```

<210> 179
<211> 250
<212> DNA
<213> Homo sapien

<400> 179

```
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct       60
ccagctgccc ccggccgggg gatgcgaggc tcggagcacc cttgcccggc tgtgattgct      120
gccaggcact gttcatctca gcttttctgt ccctttgctc ccggcaagcg cttctgctga      180
aagttcatat ctggagcctg atgtcttaac gaataaaggt cccatgctcc acccgaaaaa      240
```

aaaaaaaaaa 250

<210> 180
<211> 202
<212> DNA
<213> Homo sapien

<400> 180
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca 60
tcacccagac cccgcccctg cccgtgcccc acgctgctgc taacgacagt atgatgctta 120
ctctgctact cggaaactat ttttatgtaa ttaatgtatg ctttcttgtt tataaatgcc 180
tgatttaaaa aaaaaaaaaa aa 202

<210> 181
<211> 558
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(558)
<223> n = A,T,C or G

<400> 181
tccytttgkt naggtttkkg agacamccck agacctwaan ctgtgtcaca gacttcyngg 60
aatgtttagg cagtgctagt aatttcytcg taatgattct gttattactt tcctnattct 120
ttattcctct ttcttctgaa gattaatgaa gttgaaaatt gaggtggata aatacaaaaa 180
ggtagtgtga tagtataagt atctaagtgc agatgaaagt gtgttatata tatccattca 240
aaattatgca agttagtaat tactcagggt taactaaatt actttaatat gctgttgaac 300
ctactctgtt ccttggctag aaaaaattat aaacaggact ttgttagttt gggaagccaa 360
attgataata ttctatgttc taaaagttgg gctatacata aattattaag aaatatggaw 420
ttttattccc aggaatatgg kgttcatttt atgaatatta cscrggatag awgtwtgagt 480
aaaaycagtt ttggtwaata ygtwaatatg tcmtaaataa acaakgcttt gacttatttc 540
caaaaaaaaa aaaaaaa 558

<210> 182
<211> 479
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(479)
<223> n = A,T,C or G

<400> 182
acagggwttk grggatgcta agsccccrga rwtygtttga tccaaccctg gcttwttttc 60
agaggggaaa atggggccta gaagttacag mscatytagy tggtgcgmtg gcacccctgg 120
cstcacacag astcccgagt agctgggact acaggcacac agtcactgaa gcaggccctg 180
ttwgcaattc acgttgccac ctccaactta aacattcttc atatgtgatg tccttagtca 240
ctaaggttaa actttcccac ccagaaaagg caacttagat aaaatcttag agtactttca 300
tactmttcta agtcctcttc cagcctcact kkgagtcctm cytgggggtt gataggaant 360
ntctcttggc tttctcaata aartctctat ycatctcatg tttaatttgg tacgcatara 420
awtgstgara aaattaaaat gttctggtty mactttaaaa araaaaaaaa aaaaaaaa 479

<210> 183
<211> 384
<212> DNA

<213> Homo sapien

<400> 183
aggcgggagc agaagctaaa gccaaagccc aagaagagtg gcagtgccag cactggtgcc 60
agtaccagta ccaataacag tgccagtgcc agtgccagca ccagtggtgg cttcagtgct 120
ggtgccagcc tgaccgccac tctcacattt gggctcttcg ctggccttgg tggagctggt 180
gccagcacca gtggcagctc tggtgcctgt ggtttctcct acaagtgaga ttttagatat 240
tgttaatcct gccagtcttt ctcttcaagc cagggtgcat cctcagaaac ctactcaaca 300
cagcactcta ggcagccact atcaatcaat tgaagttgac actctgcatt aratctattt 360
gccatttcaa aaaaaaaaaa aaaa 384

<210> 184
<211> 496
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(496)
<223> n = A,T,C or G

<400> 184
accgaattgg gaccgctggc ttataagcga tcatgtyynt ccrgtatkac ctcaacgagc 60
agggagatcg agtctatacg ctgaagaaat ttgacccgat gggacaacag acctgctcag 120
cccatcctgc tcggttctcc ccagatgaca aatactctsg acaccgaatc accatcaaga 180
aacgcttcaa ggtgctcatg acccagcaac cgcgccctgt cctctgaggg tcccttaaac 240
tgatgtcttt tctgccacct gttacccctc ggagactccg taaccaaact cttcggactg 300
tgagccctga tgcctttttg ccagccatac tctttggcat ccagtctctc gtggcgattg 360
attatgcttg tgtgaggcaa tcatggtggc atcacccata aagggaacac atttgacttt 420
tttttctcat attttaaatt actacmagaw tattwmagaw waaatgawtt gaaaaactst 480
taaaaaaaaa aaaaaa 496

<210> 185
<211> 384
<212> DNA
<213> Homo sapien

<400> 185
gctggtagcc tatggcgkgg cccacggagg ggctcctgag gccacggrac agtgacttcc 60
caagtatcyt gcgcsgcgtc ttctaccgtc cctacctgca gatcttcggg cagattcccc 120
aggaggacat ggacgtggcc ctcatggagc acagcaactg ytcgtcggag cccggcttct 180
gggcacaccc tcctggggcc caggcgggca cctgcgtctc ccagtatgcc aactggctgg 240
tggtgctgct cctcgtcatc ttcctgctcg tggccaacat cctgctggtc aacttgctca 300
ttgccatgtt cagttacaca ttcggcaaag tacagggcaa cagcgatctc tactgggaag 360
gcgcagcgtt accgcctcat ccgg 384

<210> 186
<211> 577
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(577)
<223> n = A,T,C or G

<400> 186
gagttagctc ctccacaacc ttgatgaggt cgtctgcagt ggcctctcgc ttcataccgc 60

tnccatcgtc atactgtagg tttgccacca cytcctggca tcttggggcg gcntaatatt 120
ccaggaaact ctcaatcaag tcaccgtcga tgaaacctgt gggctggttc tgtcttccgc 180
tcggtgtgaa aggatctccc agaaggagtg ctcgatcttc cccacacttt tgatgacttt 240
attgagtcga ttctgcatgt ccagcaggag gttgtaccag ctctctgaca gtgaggtcac 300
cagccctatc atgccgttga mcgtgccgaa garcaccgag ccttgtgtgg gggkkgaagt 360
ctcacccaga ttctgcatta ccagagagcc gtggcaaaag acattgacaa actcgcccag 420
gtggaaaaag amcamctcct ggargtgctn gccgctcctc gtcmgttggt ggcagcgctw 480
tccttttgac acacaaacaa gttaaaggca tttcagccc ccagaaantt gtcatcatcc 540
aagatntcgc acagcactna tccagttggg attaaat 577

<210> 187
<211> 534
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(534)
<223> n = A,T,C or G

<400> 187
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgstg agaatycatw 60
actkggaaaa gmaacattaa agcctggaca ctggtattaa aattcacaat atgcaacact 120
ttaaacagtg tgtcaatctg ctcccyynac tttgtcatca ccagtctggg aakaagggta 180
tgccctattc acacctgtta aaagggcgct aagcattttt gattcaacat cttttttttt 240
gacacaagtc cgaaaaaagc aaaagtaaac agttatyaat ttgttagcca attcactttc 300
ttcatgggac agagccatyt gatttaaaaa gcaaattgca taatattgag cttygggagc 360
tgatatttga gcggaagagt agcctttcta cttcaccaga cacaactccc tttcatattg 420
ggatgttnac naaagtwatg tctctwacag atgggatgct tttgtggcaa ttctgttctg 480
aggatctccc agtttattta ccacttgcac aagaaggcgt ttcttcctc aggc 534

<210> 188
<211> 761
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(761)
<223> n = A,T,C or G

<400> 188
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg 60
tgtgtgtgcg cgcatattat atagacaggc acatcttttt tacttttgta aaagcttatg 120
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct 180
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt 240
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc ctkgackarg 300
ggggacaaag aaaagcaaaa ctgamcataa raaacaatwa cctggtgaga arttgcataa 360
acagaaatwr ggtagtatat tgaarnacag catcattaaa rmgttwtktt wttctccctt 420
gcaaaaaaca tgtacngact tcccgttgag taatgccaag ttgttttttt tatnataaaa 480
cttgcccttc attacatgtt tnaaagtggt gtggtgggcc aaaatattga aatgatggaa 540
ctgactgata aagctgtaca aataagcagt gtgcctaaca agcaacacag taatgttgac 600
atgcttaatt cacaaatgct aatttcatta taaatgtttg ctaaaataca ctttgaacta 660
tttttctgtn ttcccagagc tgagatntta gattttatgt agtatnaagt gaaaaantac 720
gaaaataata acattgaaga aaaanaaaa aaanaaaaaa a 761

<210> 189
<211> 482

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(482)
<223> n = A,T,C or G

<400> 189
```
tttttttttt tttgccgatn ctactatttt attgcaggan gtgggggtgt atgcaccgca     60
caccggggct atnagaagca agaaggaagg agggagggca cagccccttg ctgagcaaca    120
aagccgcctg ctgccttctc tgtctgtctc ctggtgcagg cacatgggga gaccttcccc    180
aaggcagggg ccaccagtcc aggggtggga atacaggggg tgggangtgt gcataagaag    240
tgataggcac aggccacccg gtacagaccc ctcggctcct gacaggtnga tttcgaccag    300
gtcattgtgc cctgcccagg cacagcgtan atctggaaaa gacagaatgc tttccttttc    360
aaatttggct ngtcatngaa ngggcanttt tccaanttng gctnggtctt ggtacncttg    420
gttcggccca gctccncgtc caaaaantat tcacccnnct ccnaattgct tgcnggnccc    480
cc                                                                   482
```

<210> 190
<211> 471
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(471)
<223> n = A,T,C or G

<400> 190
```
tttttttttt ttttaaaaca gtttttcaca acaaaattta ttagaagaat agtggttttg     60
aaaactctcg catccagtga gaactaccat acaccacatt acagctngga atgtnctcca    120
aatgtctggt caaatgatac aatggaacca ttcaatctta cacatgcacg aaagaacaag    180
cgcttttgac atacaatgca caaaaaaaaa aggggggggg gaccacatgg attaaaattt    240
taagtactca tcacatacat taagacacag ttctagtcca gtcnaaaatc agaactgcnt    300
tgaaaaattt catgtatgca atccaaccaa agaacttnat tggtgatcat gantnctcta    360
ctacatcnac cttgatcatt gccaggaacn aaaagttnaa ancacncngt acaaaaanaa    420
tctgtaattn anttcaacct ccgtacngaa aaatnttnnt tatacactcc c             471
```

<210> 191
<211> 402
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(402)
<223> n = A,T,C or G

<400> 191
```
gagggattga aggtctgttc tastgtcggm ctgttcagcc accaactcta acaagttgct     60
gtcttccact cactgtctgt aagcttttta acccagacwg tatcttcata aatagaacaa    120
attcttcacc agtcacatct tctaggacct ttttggattc agttagtata agctcttcca    180
cttcctttgt taagacttca tctggtaaag tcttaagttt tgtagaaagg aattyaattg    240
ctcgttctct aacaatgtcc tctccttgaa gtatttggct gaacaaccca cctaaagtcc    300
ctttgtgcat ccattttaaa tatacttaat agggcattgk tncactaggt taaattctgc    360
aagagtcatc tgtctgcaaa agttgcgtta gtatatctgc ca                       402
```

<210> 192
<211> 601
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(601)
<223> n = A,T,C or G

<400> 192
gagctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact 60
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac 120
atgcytyttt gaytaccgtg tgccaagtgc tggtgattct yaacacacyt ccatcccgyt 180
cttttgtgga aaaactggca cttktctgga actagcarga catcacttac aaattcaccc 240
acgagacact tgaaaggtgt aacaaagcga ytcttgcatt gctttttgtc cctccggcac 300
cagttgtcaa tactaacccg ctggtttgcc tccatcacat ttgtgatctg tagctctgga 360
tacatctcct gacagtactg aagaacttct tcttttgttt caaaagcarc tcttggtgcc 420
tgttggatca ggttcccatt tcccagtcyg aatgttcaca tggcatattt wacttcccac 480
aaaacattgc gatttgaggc tcagcaacag caaatcctgt tccggcattg gctgcaagag 540
cctcgatgta gccggccagc gccaaggcag gcgccgtgag ccccaccagc agcagaagca 600
g 601

<210> 193
<211> 608
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(608)
<223> n = A,T,C or G

<400> 193
atacagccca natcccacca cgaagatgcg cttgttgact gagaacctga tgcggtcact 60
ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcytt 120
cccaacgcag gcagmagcgg gsccggtcaa tgaactccay tcgtggcttg gggtkgacgg 180
tkaagtgcag gaagaggctg accacctcgc ggtccaccag gatgcccgac tgtgcgggac 240
ctgcagcgaa actcctcgat ggtcatgagc gggaagcgaa tgaggcccag ggccttgccc 300
agaaccttcc gcctgttctc tggcgtcacc tgcagctgct gccgctgaca ctcggcctcg 360
gaccagcgga caaacggcrt tgaacagccg cacctcacgg atgcccagtg tgtcgcgctc 420
caggammgsc accagcgtgt ccaggtcaat gtcggtgaag ccctccgcgg gtratggcgt 480
ctgcagtgtt tttgtcgatg ttctccaggc acaggctggc cagctgcggt tcatcgaaga 540
gtcgcgcctg cgtgagcagc atgaaggcgt tgtcggctcg cagttcttct tcaggaactc 600
cacgcaat 608

<210> 194
<211> 392
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(392)
<223> n = A,T,C or G

<400> 194
gaacggctgg accttgcctc gcattgtgct tgctggcagg gaataccttg gcaagcagyt 60

```
ccagtccgag cagccccaga ccgctgccgc ccgaagctaa gcctgcctct ggccttcccc    120
tccgcctcaa tgcagaacca gtagtgggag cactgtgttt agagttaaga gtgaacactg    180
tttgatttta cttgggaatt tcctctgtta tatagctttt cccaatgcta atttccaaac    240
aacaacaaca aaataacatg tttgcctgtt aagttgtata aaagtaggtg attctgtatt    300
taaagaaaat attactgtta catatactgc ttgcaatttc tgtatttatt gktnctstgg    360
aaataaatat agttattaaa ggttgtcant cc                                  392
```

<210> 195
<211> 502
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(502)
<223> n = A,T,C or G

<400> 195

```
ccsttkgagg ggtkaggkyc cagttyccga gtggaagaaa caggccagga gaagtgcgtg     60
ccgagctgag gcagatgttc ccacagtgac ccccagagcc stgggstata gtytctgacc    120
cctcncaagg aaagaccacs ttctggggac atgggctgga gggcaggacc tagaggcacc    180
aagggaaggc cccattccgg ggstgttccc cgaggaggaa gggaaggggc tctgtgtgcc    240
ccccasgagg aagaggccct gagtcctggg atcagacacc ccttcacgtg tatccccaca    300
caaatgcaag ctcaccaagg tcccctctca gtccccttcc stacaccctg amcggccact    360
gscscacacc cacccagagc acgccacccg ccatggggar tgtgctcaag gartcgcngg    420
gcarcgtgga catctngtcc cagaaggggg cagaatctcc aatagangga ctgarcmstt    480
gctnanaaaa aaaaanaaaa aa                                             502
```

<210> 196
<211> 665
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(665)
<223> n = A,T,C or G

<400> 196

```
ggttacttgg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc     60
cctctggaag ccttgcgcag agcggacttt gtaattgttg gagaataact gctgaatttt    120
wagctgtttk gagttgatts gcaccactgc acccacaact tcaatatgaa aacyawttga    180
actwatttat tatcttgtga aaagtataac aatgaaaatt ttgttcatac tgtattkatc    240
aagtatgatg aaaagcaawa gatatatatt cttttattat gttaaattat gattgccatt    300
attaatcggc aaaatgtgga gtgtatgttc ttttcacagt aatatatgcc ttttgtaact    360
tcacttggtt attttattgt aaatgartta caaaattctt aatttaagar aatggtatgt    420
watatttatt tcattaattt ctttcctkgt ttacgtwaat tttgaaaaga wtgcatgatt    480
tcttgacaga aatcgatctt gatgctgtgg aagtagtttg acccacatcc ctatgagttt    540
ttcttagaat gtataaaggt tgtagcccat cnaacttcaa agaaaaaaat gaccacatac    600
tttgcaatca ggctgaaatg tggcatgctn ttctaattcc aactttataa actagcaaan    660
aagtg                                                                665
```

<210> 197
<211> 492
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(492)
<223> n = A,T,C or G

<400> 197
```
ttttnttttt ttttttttgc aggaaggatt ccatttattg tggatgcatt ttcacaatat      60
atgtttattg gagcgatcca ttatcagtga aaagtatcaa gtgtttataa natttttagg     120
aaggcagatt cacagaacat gctngtcngc ttgcagtttt acctcgtana gatnacagag     180
aattatagtc naaccagtaa acnaggaatt tacttttcaa aagattaaat ccaaactgaa     240
caaaattcta ccctgaaact tactccatcc aaatattgga ataanagtca gcagtgatac     300
attctcttct gaactttaga ttttctagaa aaatatgtaa tagtgatcag gaagagctct     360
tgttcaaaag tacaacnaag caatgttccc ttaccatagg ccttaattca aactttgatc     420
catttcactc ccatcacggg agtcaatgct acctgggaca cttgtatttt gttcatnctg     480
ancntggctt aa                                                         492
```

<210> 198
<211> 478
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(478)
<223> n = A,T,C or G

<400> 198
```
tttnttttgn atttcantct gtannaanta ttttcattat gtttattana aaaatatnaa      60
tgtntccacn acaaatcatn ttacntnagt aagaggccan ctacattgta caacatacac     120
tgagtatatt ttgaaaagga caagtttaaa gtanacncat attgccganc atancacatt     180
tatacatggc ttgattgata tttagcacag canaaactga gtgagttacc agaaanaaat     240
natatatgtc aatcngattt aagatacaaa acagatccta tggtacatan catcntgtag     300
gagttgtggc tttatgttta ctgaaagtca atgcagttcc tgtacaaaga gatggccgta     360
agcattctag tacctctact ccatggttaa gaatcgtaca cttatgttta catatgtnca     420
gggtaagaat tgtgttaagt naanttatgg agaggtccan gagaaaaatt tgatncaa       478
```

<210> 199
<211> 482
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(482)
<223> n = A,T,C or G

<400> 199
```
agtgacttgt cctccaacaa aaccccttga tcaagtttgt ggcactgaca atcagaccta      60
tgctagttcc tgtcatctat tcgctactaa atgcagactg gaggggacca aaaaggggca     120
tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga     180
agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta     240
tgaagccnac tctgaacacg ctggttatct nagatgagaa ncagagaaat aaagtcnaga     300
aaatttacct ggangaaaag aggctttngg ctggggacca tcccattgaa ccttctctta     360
anggacttta agaanaaact accacatgtn tgtngtatcc tggtgccngg ccgtttantg     420
aacntngacn ncacccttnt ggaatanant cttgacngcn tcctgaactt gctcctctgc     480
ga                                                                    482
```

<210> 200
<211> 270

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(270)
<223> n = A,T,C or G

<400> 200
cggccgcaag tgcaactcca gctggggccg tgcggacgaa gattctgcca gcagttggtc 60
cgactgcgac gacggcggcg gcgacagtcg caggtgcagc gcgggcgcct ggggtcttgc 120
aaggctgagc tgacgccgca gaggtcgtgt cacgtcccac gaccttgacg ccgtcgggga 180
cagccggaac agagcccggt gaangcggga ggcctcgggg agcccctcgg gaagggcggc 240
ccgagagata cgcaggtgca ggtggccgcc 270

<210> 201
<211> 419
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(419)
<223> n = A,T,C or G

<400> 201
tttttttttt ttttggaatc tactgcgagc acagcaggtc agcaacaagt ttattttgca 60
gctagcaagg taacagggta gggcatggtt acatgttcag gtcaacttcc tttgtcgtgg 120
ttgattggtt tgtctttatg gggcggggt ggggtagggg aaancgaagc anaantaaca 180
tggagtgggt gcaccctccc tgtagaacct ggttacnaaa gcttggggca gttcacctgg 240
tctgtgaccg tcattttctt gacatcaatg ttattagaag tcaggatatc ttttagagag 300
tccactgtnt ctggagggag attagggttt cttgccaana tccaancaaa atccacntga 360
aaaagttgga tgatncangt acngaatacc ganggcatan ttctcatant cggtggcca 419

<210> 202
<211> 509
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(509)
<223> n = A,T,C or G

<400> 202
tttntttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 60
tggcacttaa tccattttta tttcaaaatg tctacaaant ttnaatncnc cattatacng 120
gtnattttnc aaaatctaaa nnttattcaa atntnagcca aantccttac ncaaatnnaa 180
tacncncaaa aatcaaaaat atacntntct ttcagcaaac ttngttacat aaattaaaaa 240
aatatatacg gctggtgttt tcaaagtaca attatcttaa cactgcaaac atntttnnaa 300
ggaactaaaa taaaaaaaaa cactnccgca aaggttaaag ggaacaacaa attcntttta 360
caacancnnc nattataaaa atcatatctc aaatcttagg ggaatatata cttcacacng 420
ggatcttaac ttttactnca ctttgtttat ttttttanaa ccattgtntt gggcccaaca 480
caatggnaat nccnccncnc tggactagt 509

<210> 203
<211> 583
<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(583)
<223> n = A,T,C or G

<400> 203
tttttttttt tttttttga cccccctctt ataaaaaaca agttaccatt ttattttact 60
tacacatatt tattttataa ttggtattag atattcaaaa ggcagctttt aaaatcaaac 120
taaatggaaa ctgccttaga tacataattc ttaggaatta gcttaaaatc tgcctaaagt 180
gaaaatcttc tctagctctt ttgactgtaa atttttgact cttgtaaaac atccaaattc 240
atttttcttg tctttaaaat tatctaatct ttccattttt tccctattcc aagtcaattt 300
gcttctctag cctcatttcc tagctcttat ctactattag taagtggctt ttttcctaaa 360
agggaaaaca ggaagagana atggcacaca aaacaaacat tttatattca tatttctacc 420
tacgttaata aaatagcatt ttgtgaagcc agctcaaaag aaggcttaga tccttttatg 480
tccattttag tcactaaacg atatcnaaag tgccagaatg caaaaggttt gtgaacattt 540
attcaaaagc taatataaga tatttcacat actcatcttt ctg 583

<210> 204
<211> 589
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(589)
<223> n = A,T,C or G

<400> 204
ttttttttnt tttttttttt ttttttnctc ttcttttttt ttganaatga ggatcgagtt 60
tttcactctc tagatagggc atgaagaaaa ctcatctttc cagctttaaa ataacaatca 120
aatctcttat gctatatcat attttaagtt aaactaatga gtcactggct tatcttctcc 180
tgaaggaaat ctgttcattc ttctcattca tatagttata tcaagtacta ccttgcatat 240
tgagaggttt ttcttctcta tttacacata tatttccatg tgaatttgta tcaaaccttt 300
atttcatgc aaactagaaa ataatgtntt cttttgcata agagaagaga acaatatnag 360
cattacaaaa ctgctcaaat tgtttgttaa gnttatccat tataattagt tnggcaggag 420
ctaatacaaa tcacatttac ngacnagcaa taataaaact gaagtaccag ttaaatatcc 480
aaaataatta aaggaacatt tttagcctgg gtataattag ctaattcact ttacaagcat 540
ttattnagaa tgaattcaca tgttattatt ccntagccca acacaatgg 589

<210> 205
<211> 545
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(545)
<223> n = A,T,C or G

<400> 205
tttttntttt ttttttcagt aataatcaga acaatattta tttttatatt taaaattcat 60
agaaaagtgc cttacattta ataaaagttt gtttctcaaa gtgatcagag gaattagata 120
tngtcttgaa caccaatatt aatttgagga aaatacacca aaatacatta agtaaattat 180
ttaagatcat agagcttgta agtgaaaaga taaaatttga cctcagaaac tctgagcatt 240
aaaaatccac tattagcaaa taaattacta tggacttctt gctttaattt tgtgatgaat 300
atggggtgtc actggtaaac caacacattc tgaaggatac attacttagt gatagattct 360

tatgtacttt gctanatnac gtggatatga gttgacaagt ttctctttct tcaatctttt 420
aaggggcnga ngaaatgagg aagaaaagaa aaggattacg catactgttc tttctatngg 480
aaggattaga tatgtttcct ttgccaatat taaaaaaata ataatgttta ctactagtga 540
aaccc 545

<210> 206
<211> 487
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(487)
<223> n = A,T,C or G

<400> 206
tttttttttt ttttttagtc aagtttctna tttttattat aattaaagtc ttggtcattt 60
catttattag ctctgcaact tacatattta aattaaagaa acgttnttag acaactgtna 120
caatttataa atgtaaggtg ccattattga gtanatatat tcctccaaga gtggatgtgt 180
cccttctccc accaactaat gaancagcaa cattagttta attttattag tagatnatac 240
actgctgcaa acgctaattc tcttctccat ccccatgtng atattgtgta tatgtgtgag 300
ttggtnagaa tgcatcanca atctnacaat caacagcaag atgaagctag gcntgggctt 360
tcggtgaaaa tagactgtgt ctgtctgaat caaatgatct gacctatcct cggtggcaag 420
aactcttcga accgcttcct caaaggcngc tgccacattt gtggcntctn ttgcacttgt 480
ttcaaaa 487

<210> 207
<211> 332
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(332)
<223> n = A,T,C or G

<400> 207
tgaattggct aaaagactgc atttttanaa ctagcaactc ttatttcttt cctttaaaaa 60
tacatagcat taaatcccaa atcctattta aagacctgac agcttgagaa ggtcactact 120
gcatttatag gaccttctgg tggttctgct gttacntttg aantctgaca atccttgana 180
atctttgcat gcagaggagg taaaaggtat tggattttca cagaggaana acacagcgca 240
gaaatgaagg ggccaggctt actgagcttg tccactggag ggctcatggg tgggacatgg 300
aaaagaaggc agcctaggcc ctggggagcc ca 332

<210> 208
<211> 524
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(524)
<223> n = A,T,C or G

<400> 208
agggcgtggt gcggagggcg ttactgtttt gtctcagtaa caataaatac aaaaagactg 60
gttgtgttcc ggccccatcc aaccacgaag ttgatttctc ttgtgtgcag agtgactgat 120
tttaaaggac atggagcttg tcacaatgtc acaatgtcac agtgtgaagg gcacactcac 180

```
tcccgcgtga ttcacattta gcaaccaaca atagctcatg agtccatact tgtaaatact     240
tttggcagaa tacttnttga aacttgcaga tgataactaa gatccaagat atttcccaaa     300
gtaaatagaa gtgggtcata atattaatta cctgttcaca tcagcttcca tttacaagtc     360
atgagcccag acactgacat caaactaagc ccacttagac tcctcaccac cagtctgtcc     420
tgtcatcaga caggaggctg tcaccttgac caaattctca ccagtcaatc atctatccaa     480
aaaccattac ctgatccact tccggtaatg caccaccttg gtga                     524

      <210> 209
      <211> 159
      <212> DNA
      <213> Homo sapien

      <400> 209
gggtgaggaa atccagagtt gccatggaga aaattccagt gtcagcattc ttgctccttg      60
tggccctctc ctacactctg gccagagata ccacagtcaa acctggagcc aaaaaggaca     120
caaaggactc tcgacccaaa ctgccccaga ccctctcca                           159

      <210> 210
      <211> 256
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(256)
      <223> n = A,T,C or G

      <400> 210
actccctggc agacaaaggc agaggagaga gctctgttag ttctgtgttg ttgaactgcc      60
actgaatttc tttccacttg gactattaca tgccanttga gggactaatg gaaaaacgta     120
tggggagatt ttanccaatt tangtntgta aatggggaga ctggggcagg cgggagagat     180
ttgcagggtg naaatgggan ggctggtttg ttanatgaac agggacatag gaggtaggca     240
ccaggatgct aaatca                                                    256

      <210> 211
      <211> 264
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(264)
      <223> n = A,T,C or G

      <400> 211
acattgtttt tttgagataa agcattgaga gagctctcct taacgtgaca caatggaagg      60
actggaacac atacccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt     120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gttaaggaga     180
ggggagatac attcngaaag aggactgaaa gaaatactca agtnggaaaa cagaaaaaga     240
aaaaaaggag caaatgagaa gcct                                           264

      <210> 212
      <211> 328
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
```

<222> (1)...(328)
<223> n = A,T,C or G

<400> 212
acccaaaaat ccaatgctga atatttggct tcattattcc canattcttt gattgtcaaa 60
ggatttaatg ttgtctcagc ttgggcactt cagttaggac ctaaggatgc cagccggcag 120
gtttatatat gcagcaacaa tattcaagcg cgacaacagg ttattgaact tgcccgccag 180
ttnaatttca ttcccattga cttgggatcc ttatcatcag ccagagagat tgaaaattta 240
cccctacnac tctttactct ctgganaggg ccagtggtgg tagctataag cttggccaca 300
tttttttttc ctttattcct ttgtcaga 328

<210> 213
<211> 250
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(250)
<223> n = A,T,C or G

<400> 213
acttatgagc agagcgacat atccnagtgt agactgaata aaactgaatt ctctccagtt 60
taaagcattg ctcactgaag ggatagaagt gactgccagg agggaaagta agccaaggct 120
cattatgcca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt 180
ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatatc tctctnacct 240
tctcatcggt 250

<210> 214
<211> 444
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(444)
<223> n = A,T,C or G

<400> 214
acccagaatc caatgctgaa tatttggctt cattattccc agattctttg attgtcaaag 60
gatttaatgt tgtctcagct tgggcacttc agttaggacc taaggatgcc agccggcagg 120
tttatatatg cagcaacaat attcaagcgc gacaacaggt tattgaactt gcccgccagt 180
tgaatttcat tcccattgac ttgggatcct tatcatcagc canagagatt gaaaatttac 240
ccctacgact ctttactctc tggagagggc cagtggtggt agctataagc ttggccacat 300
ttttttttcc tttattcctt tgtcagagat gcgattcatc catatgctan aaaccaacag 360
agtgactttt acaaaattcc tataganatt gtgaataaaa ccttacctat agttgccatt 420
actttgctct ccctaatata cctc 444

<210> 215
<211> 366
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(366)
<223> n = A,T,C or G

<400> 215
acttatgagc agagcgacat atccaagtgt anactgaata aaactgaatt ctctccagtt 60
taaagcattg ctcactgaag ggatagaagt gactgccagg agggaaagta agccaaggct 120
cattatgcca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt 180
ttcaatattt gcatgaacct gctgataagc catgttgaga aacaaatatc tctctgacct 240
tctcatcggt aagcagaggc tgtaggcaac atggaccata gcgaanaaaa aacttagtaa 300
tccaagctgt tttctacact gtaaccaggt ttccaaccaa ggtggaaatc tcctatactt 360
ggtgcc 366

<210> 216
<211> 260
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(260)
<223> n = A,T,C or G

<400> 216
ctgtataaac agaactccac tgcangaggg agggccgggc caggagaatc tccgcttgtc 60
caagacaggg gcctaaggag ggtctccaca ctgctnntaa gggctnttnc attttttat 120
taataaaaag tnnaaaaggc ctcttctcaa cttttttccc ttnggctgga aaatttaaaa 180
atcaaaaatt tcctnaagtt ntcaagctat catatatact ntatcctgaa aaagcaacat 240
aattcttcct tccctccttt 260

<210> 217
<211> 262
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(262)
<223> n = A,T,C or G

<400> 217
acctacgtgg gtaagtttan aaatgttata atttcaggaa naggaacgca tataattgta 60
tcttgcctat aattttctat tttaataagg aaatagcaaa ttggggtggg gggaatgtag 120
ggcattctac agtttgagca aaatgcaatt aaatgtggaa ggacagcact gaaaaatttt 180
atgaataatc tgtatgatta tatgtctcta gagtagattt ataattagcc acttacccta 240
atatccttca tgcttgtaaa gt 262

<210> 218
<211> 205
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(205)
<223> n = A,T,C or G

<400> 218
accaaggtgg tgcattaccg gaantggatc aangacacca tcgtggccaa cccctgagca 60
cccctatcaa ctcccttttg tagtaaactt ggaaccttgg aaatgaccag gccaagactc 120
aggcctcccc agttctactg acctttgtcc ttangtntna ngtccagggt tgctaggaaa 180
anaaatcagc agacacaggt gtaaa 205

<210> 219
<211> 114
<212> DNA
<213> Homo sapien

<400> 219
tactgttttg tctcagtaac aataaataca aaaagactgg ttgtgttccg gccccatcca 60
accacgaagt tgatttctct tgtgtgcaga gtgactgatt ttaaaggaca tgga 114

<210> 220
<211> 93
<212> DNA
<213> Homo sapien

<400> 220
actagccagc acaaaaggca gggtagcctg aattgctttc tgctctttac atttctttta 60
aaataagcat ttagtgctca gtccctactg agt 93

<210> 221
<211> 167
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(167)
<223> n = A,T,C or G

<400> 221
actangtgca ggtgcgcaca aatatttgtc gatattccct tcatcttgga ttccatgagg 60
tcttttgccc agcctgtggc tctactgtag taagtttctg ctgatgagga gccagnatgc 120
cccccactac cttccctgac gctccccana aatcacccaa cctctgt 167

<210> 222
<211> 351
<212> DNA
<213> Homo sapien

<400> 222
agggcgtggt gcggagggcg gtactgacct cattagtagg aggatgcatt ctggcacccc 60
gttcttcacc tgtcccccaa tccttaaaag gccatactgc ataaagtcaa caacagataa 120
atgtttgctg aattaaagga tggatgaaaa aaattaataa tgaatttttg cataatccaa 180
ttttctcttt tatatttcta gaagaagttt ctttgagcct attagatccc gggaatcttt 240
taggtgagca tgattagaga gcttgtaggt tgcttttaca tatatctggc atatttgagt 300
ctcgtatcaa aacaatagat tggtaaaggt ggtattattg tattgataag t 351

<210> 223
<211> 383
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(383)
<223> n = A,T,C or G

<400> 223

aaaacaaaca aacaaaaaaa acaattcttc attcagaaaa attatcttag ggactgatat 60
tggtaattat ggtcaattta atwrtrttkt ggggcatttc cttacattgt cttgacaaga 120
ttaaaatgtc tgtgccaaaa ttttgtattt tatttggaga cttcttatca aaagtaatgc 180
tgccaaagga agtctaagga attagtagtg ttcccmtcac ttgtttggag tgtgctattc 240
taaaagattt tgatttcctg gaatgacaat tatattttaa ctttggtggg ggaaanagtt 300
ataggaccac agtcttcact tctgatactt gtaaattaat cttttattgc acttgttttg 360
accattaagc tatatgttta aaa 383

<210> 224
<211> 320
<212> DNA
<213> Homo sapien

<400> 224
cccctgaagg cttcttgtta gaaaatagta cagttacaac caataggaac aacaaaaaga 60
aaaagtttgt gacattgtag tagggagtgt gtacccctta ctccccatca aaaaaaaaat 120
ggatacatgg ttaaaggata raagggcaat attttatcat atgttctaaa agagaaggaa 180
gagaaaatac tactttctcr aaatggaagc ccttaaaggt gctttgatac tgaaggacac 240
aaatgtggcc gtccatcctc ctttaragtt gcatgacttg gacacggtaa ctgttgcagt 300
tttaractcm gcattgtgac 320

<210> 225
<211> 1214
<212> DNA
<213> Homo sapien

<400> 225
gaggactgca gcccgcactc gcagccctgg caggcggcac tggtcatgga aaacgaattg 60
ttctgctcgg gcgtcctggt gcatccgcag tgggtgctgt cagccgcaca ctgtttccag 120
aactcctaca ccatcgggct gggcctgcac agtcttgagg ccgaccaaga gccagggagc 180
cagatggtgg aggccagcct ctccgtacgg cacccagagt acaacagacc cttgctcgct 240
aacgacctca tgctcatcaa gttggacgaa tccgtgtccg agtctgacac catccggagc 300
atcagcattg cttcgcagtg ccctaccgcg gggaactctt gcctcgtttc tggctggggt 360
ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg tgaacgtgtc ggtggtgtct 420
gaggaggtct gcagtaagct ctatgacccg ctgtaccacc ccagcatgtt ctgcgccggc 480
ggagggcaag accagaagga ctcctgcaac ggtgactctg gggggcccct gatctgcaac 540
gggtacttgc agggccttgt gtctttcgga aaagccccgt gtggccaagt tggcgtgcca 600
ggtgtctaca ccaacctctg caaattcact gagtggatag agaaaaccgt ccaggccagt 660
taactctggg gactgggaac ccatgaaatt gaccccccaaa tacatcctgc ggaaggaatt 720
caggaatatc tgttcccagc ccctcctccc tcaggcccag gagtccaggc ccccagcccc 780
tcctccctca aaccaagggt acagatcccc agcccctcct ccctcagacc caggagtcca 840
gacccccccag cccctcctcc ctcagaccca ggagtccagc ccctcctccc tcagacccag 900
gagtccagac cccccagccc ctcctccctc agacccaggg gtccaggccc ccaacccctc 960
ctccctcaga ctcagaggtc caagccccca acccctcctt ccccagaccc agaggtccag 1020
gtcccagccc ctcctccctc agacccagcg gtccaatgcc acctagactc tccctgtaca 1080
cagtgccccc ttgtggcacg ttgacccaac cttaccagtt ggtttttcat tttttgtccc 1140
tttcccctag atccagaaat aaagtctaag agaagcgcaa aaaaaaaaaa aaaaaaaaaa 1200
aaaaaaaaaa aaaa 1214

<210> 226
<211> 119
<212> DNA
<213> Homo sapien

<400> 226
acccagtatg tgcagggaga cggaacccca tgtgacagcc cactccacca gggttcccaa 60
agaacctggc ccagtcataa tcattcatcc tgacagtggc aataatcacg ataaccagt 119

<210> 227
<211> 818
<212> DNA
<213> Homo sapien

<400> 227
acaattcata gggacgacca atgaggacag ggaatgaacc cggctctccc ccagccctga 60
tttttgctac atatggggtc ccttttcatt ctttgcaaaa acactgggtt ttctgagaac 120
acggacggtt cttagcacaa tttgtgaaat ctgtgtaraa ccgggctttg caggggagat 180
aattttcctc ctctggagga aaggtggtga ttgacaggca gggagacagt gacaaggcta 240
gagaaagcca cgctcggcct tctctgaacc aggatggaac ggcagacccc tgaaaacgaa 300
gcttgtcccc ttccaatcag ccacttctga gaacccccat ctaacttcct actggaaaag 360
agggcctcct caggagcagt ccaagagttt tcaaagataa cgtgacaact accatctaga 420
ggaaagggtg caccctcagc agagaagccg agagcttaac tctggtcgtt tccagagaca 480
acctgctggc tgtcttggga tgcgcccagc ctttgagagg ccactacccc atgaacttct 540
gccatccact ggacatgaag ctgaggacac tgggcttcaa cactgagttg tcatgagagg 600
gacaggctct gccctcaagc cggctgaggg cagcaaccac tctcctcccc tttctcacgc 660
aaagccattc ccacaaatcc agaccatacc atgaagcaac gagacccaaa cagtttggct 720
caagaggata tgaggactgt ctcagcctgg ctttgggctg acaccatgca cacacacaag 780
gtccacttct aggttttcag cctagatggg agtcgtgt 818

<210> 228
<211> 744
<212> DNA
<213> Homo sapien

<400> 228
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gtcatgacgt ttgacatacc tttggaacga gcctcctcct tggaagatgg aagaccgtgt 120
tcgtggccga cctggcctct cctggcctgt ttcttaagat gcggagtcac atttcaatgg 180
taggaaaagt ggcttcgtaa aatagaagag cagtcactgt ggaactacca aatggcgaga 240
tgctcggtgc acattggggt gctttgggat aaaagattta tgagccaact attctctggc 300
accagattct aggccagttt gttccactga agcttttccc acagcagtcc acctctgcag 360
gctggcagct gaatggcttg ccggtggctc tgtggcaaga tcacactgag atcgatgggt 420
gagaaggcta ggatgcttgt ctagtgttct tagctgtcac gttggctcct tccaggttgg 480
ccagacggtg ttggccactc ccttctaaaa cacaggcgcc ctcctggtga cagtgacccg 540
ccgtggtatg ccttggccca ttccagcagt cccagttatg catttcaagt ttggggtttg 600
ttcttttcgt taatgttcct ctgtgttgtc agctgtcttc atttcctggg ctaagcagca 660
ttgggagatg tggaccagag atccactcct taagaaccag tggcgaaaga cactttcttt 720
cttcactctg aagtagctgg tggt 744

<210> 229
<211> 300
<212> DNA
<213> Homo sapien

<400> 229
cgagtctggg ttttgtctat aaagtttgat ccctcctttt ctcatccaaa tcatgtgaac 60
cattacacat cgaaataaaa gaaaggtggc agacttgccc aacgccaggc tgacatgtgc 120
tgcagggttg ttgtttttta attattattg ttagaaacgt cacccacagt ccctgttaat 180
ttgtatgtga cagccaactc tgagaaggtc ctatttttcc acctgcagag gatccagtct 240
cactaggctc ctccttgccc tcacactgga gtctccgcca gtgtgggtgc ccactgacat 300

<210> 230
<211> 301
<212> DNA
<213> Homo sapien

<400> 230
cagcagaaca aatacaaata tgaagagtgc aaagatctca taaaatctat gctgaggaat 60
gagcgacagt tcaaggagga gaagcttgca gagcagctca agcaagctga ggagctcagg 120
caatataaag tcctggttca cactcaggaa cgagagctga cccagttaag ggagaagttg 180
cgggaaggga gagatgcctc cctctcattg aatgagcatc tccaggccct cctcactccg 240
gatgaaccgg acaagtccca ggggcaggac ctccaagaaa cagacctcgg ccgcgaccac 300
g 301

<210> 231
<211> 301
<212> DNA
<213> Homo sapien

<400> 231
gcaagcacgc tggcaaatct ctgtcaggtc agctccagag aagccattag tcattttagc 60
caggaactcc aagtccacat ccttggcaac tggggacttg cgcaggttag ccttgaggat 120
ggcaacacgg gacttctcat caggaagtgg gatgtagatg agctgatcaa gacggccagg 180
tctgaggatg gcaggatcaa tgatgtcagg ccggttggta ccgccaatga tgaacacatt 240
tttttttgtg gacatgccat ccatttctgt caggatctgg ttgatgactc ggtcagcagc 300
c 301

<210> 232
<211> 301
<212> DNA
<213> Homo sapien

<400> 232
agtaggtatt tcgtgagaag ttcaacacca aaactggaac atagttctcc ttcaagtgtt 60
ggcgacagcg gggcttcctg attctggaat ataactttgt gtaaattaac agccacctat 120
agaagagtcc atctgctgtg aaggagagac agagaactct gggttccgtc gtcctgtcca 180
cgtgctgtac caagtgctgg tgccagcctg ttacctgttc tcactgaaaa tctggctaat 240
gctcttgtgt atcacttctg attctgacaa tcaatcaatc aatggcctag agcactgact 300
g 301

<210> 233
<211> 301
<212> DNA
<213> Homo sapien

<400> 233
atgactgact tcccagtaag gctctctaag gggtaagtag gaggatccac aggatttgag 60
atgctaaggc cccagagatc gtttgatcca accctcttat tttcagaggg gaaaatgggg 120
cctagaagtt acagagcatc tagctggtgc gctggcaccc ctggcctcac acagactccc 180
gagtagctgg gactacaggc acacagtcac tgaagcaggc cctgttagca attctatgcg 240
tacaaattaa catgagatga gtagagactt tattgagaaa gcaagagaaa atcctatcaa 300
c 301

<210> 234
<211> 301
<212> DNA
<213> Homo sapien

<400> 234
aggtcctaca catcgagact catccatgat tgatatgaat ttaaaaatta caagcaaaga 60
cattttattc atcatgatgc tttcttttgt ttcttctttt cgttttcttc tttttctttt 120
tcaatttcag caacatactt ctcaatttct tcaggattta aaatcttgag ggattgatct 180
cgcctcatga cagcaagttc aatgttttg ccacctgact gaaccacttc caggagtgcc 240
ttgatcacca gcttaatggt cagatcatct gcttcaatgg cttcgtcagt atagttcttc 300

t 301

<210> 235
<211> 283
<212> DNA
<213> Homo sapien

<400> 235
tggggctgtg catcaggcgg gtttgagaaa tattcaattc tcagcagaag ccagaatttg 60
aattccctca tcttttaggg aatcatttac caggtttgga gaggattcag acagctcagg 120
tgctttcact aatgtctctg aacttctgtc cctctttgtt catggatagt ccaataaata 180
atgttatctt tgaactgatg ctcataggag agaatataag aactctgagt gatatcaaca 240
ttagggattc aaagaaatat tagatttaag ctcacactgg tca 283

<210> 236
<211> 301
<212> DNA
<213> Homo sapien

<400> 236
aggtcctcca ccaactgcct gaagcacggt taaaattggg aagaagtata gtgcagcata 60
aatactttta aatcgatcag atttccctaa cccacatgca atcttcttca ccagaagagg 120
tcggagcagc atcattaata ccaagcagaa tgcgtaatag ataaatacaa tggtatatag 180
tgggtagacg gcttcatgag tacagtgtac tgtggtatcg taatctggac ttgggttgta 240
aagcatcgtg taccagtcag aaagcatcaa tactcgacat gaacgaatat aaagaacacc 300
a 301

<210> 237
<211> 301
<212> DNA
<213> Homo sapien

<400> 237
cagtggtagt ggtggtggac gtggcgttgg tcgtggtgcc ttttttggtg cccgtcacaa 60
actcaatttt tgttcgctcc tttttggcct tttccaattt gtccatctca attttctggg 120
ccttggctaa tgcctcatag taggagtcct cagaccagcc atggggatca aacatatcct 180
ttgggtagtt ggtgccaagc tcgtcaatgg cacagaatgg atcagcttct cgtaaatcta 240
gggttccgaa attctttctt cctttggata atgtagttca tatccattcc ctcctttatc 300
t 301

<210> 238
<211> 301
<212> DNA
<213> Homo sapien

<400> 238
gggcaggttt tttttttttt ttttttgatg gtgcagaccc ttgctttatt tgtctgactt 60
gttcacagtt cagccccctg ctcagaaaac caacgggcca gctaaggaga ggaggaggca 120
ccttgagact tccggagtcg aggctctcca gggttcccca gcccatcaat cattttctgc 180
accccctgcc tgggaagcag ctccctgggg ggtgggaatg ggtgactaga agggatttca 240
gtgtgggacc cagggtctgt tcttcacagt aggaggtgga agggatgact aatttcttta 300
t 301

<210> 239
<211> 239
<212> DNA
<213> Homo sapien

<400> 239
ataagcagct agggaattct ttatttagta atgtcctaac ataaaagttc acataactgc 60
ttctgtcaaa ccatgatact gagctttgtg acaacccaga aataactaag agaaggcaaa 120
cataatacct tagagatcaa gaaacattta cacagttcaa ctgtttaaaa atagctcaac 180
attcagccag tgagtagagt gtgaatgcca gcatacacag tatacaggtc cttcaggga 239

<210> 240
<211> 300
<212> DNA
<213> Homo sapien

<400> 240
ggtcctaatg aagcagcagc ttccacattt taacgcaggt ttacggtgat actgtccttt 60
gggatctgcc ctccagtgga accttttaag gaagaagtgg gcccaagcta agttccacat 120
gctgggtgag ccagatgact tctgttccct ggtcactttc ttcaatgggg cgaatggggg 180
ctgccaggtt tttaaaatca tgcttcatct tgaagcacac ggtcacttca ccctcctcac 240
gctgtgggtg tactttgatg aaaataccca ctttgttggc ctttctgaag ctataatgtc 300

<210> 241
<211> 301
<212> DNA
<213> Homo sapien

<400> 241
gaggtctggt gctgaggtct ctgggctagg aagaggagtt ctgtggagct ggaagccaga 60
cctctttgga ggaaactcca gcagctatgt tggtgtctct gagggaatgc aacaaggctg 120
ctcctccatg tattggaaaa ctgcaaactg gactcaactg gaaggaagtg ctgctgccag 180
tgtgaagaac cagcctgagg tgacagaaac ggaagcaaac aggaacagcc agtcttttct 240
tcctcctcct gtcatacggt ctctctcaag catcctttgt tgtcaggggc ctaaaggga 300
g 301

<210> 242
<211> 301
<212> DNA
<213> Homo sapien

<400> 242
ccgaggtcct gggatgcaac caatcactct gtttcacgtg acttttatca ccatacaatt 60
tgtggcattt cctcattttc tacattgtag aatcaagagt gtaaataaat gtatatcgat 120
gtcttcaaga atatatcatt cctttttcac tagaacccat tcaaaatata agtcaagaat 180
cttaatatca acaaatatat caagcaaact ggaaggcaga ataactacca taatttagta 240
taagtaccca aagttttata aatcaaaagc cctaatgata accattttta gaattcaatc 300
a 301

<210> 243
<211> 301
<212> DNA
<213> Homo sapien

<400> 243
aggtaagtcc cagtttgaag ctcaaaagat ctggtatgag cataggctca tcgacgacat 60
ggtggcccaa gctatgaaat cagagggagg cttcatctgg gcctgtaaaa actatgatgg 120
tgacgtgcag tcggactctg tggcccaagg gtatggctct ctcggcatga tgaccagcgt 180
gctggtttgt ccagatggca agacagtaga agcagaggct gcccacggga ctgtaacccg 240
tcactaccgc atgttccaga aaggacagga gacgtccacc aatcccattg cttccatttt 300
t 301

<210> 244

<211> 300
<212> DNA
<213> Homo sapien

<400> 244
gctggtttgc aagaatgaaa tgaatgattc tacagctagg acttaacctt gaaatggaaa 60
gtcatgcaat cccatttgca ggatctgtct gtgcacatgc ctctgtagag agcagcattc 120
ccagggacct tggaaacagt tgacactgta aggtgcttgc tccccaagac acatcctaaa 180
aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc ccttcttatt tatgtgaaca 240
actgtttgtc ttttgtgtat ctttttaaa ctgtaaagtt caattgtgaa aatgaatatc 300

<210> 245
<211> 301
<212> DNA
<213> Homo sapien

<400> 245
gtctgagtat ttaaaatgtt attgaaatta tccccaacca atgttagaaa agaaagaggt 60
tatatactta gataaaaaat gaggtgaatt actatccatt gaaatcatgc tcttagaatt 120
aaggccagga gatattgtca ttaatgtara cttcaggaca ctagagtata gcagccctat 180
gttttcaaag agcagagatg caattaaata ttgtttagca tcaaaaaggc cactcaatac 240
agctaataaa atgaaagacc taatttctaa agcaattctt tataatttac aaagttttaa 300
g 301

<210> 246
<211> 301
<212> DNA
<213> Homo sapien

<400> 246
ggtctgtcct acaatgcctg cttcttgaaa gaagtcggca ctttctagaa tagctaaata 60
acctgggctt attttaaaga actatttgta gctcagattg gttttcctat ggctaaaata 120
agtgcttctt gtgaaaatta aataaaacag ttaattcaaa gccttgatat atgttaccac 180
taacaatcat actaaatata ttttgaagta caaagtttga catgctctaa agtgacaacc 240
caaatgtgtc ttacaaaaca cgttcctaac aaggtatgct ttacactacc aatgcagaaa 300
c 301

<210> 247
<211> 301
<212> DNA
<213> Homo sapien

<400> 247
aggtcctttg gcagggctca tggatcagag ctcaaactgg agggaaaggc atttcgggta 60
gcctaagagg gcgactggcg gcagcacaac caaggaaggc aaggttgttt cccccacgct 120
gtgtcctgtg ttcaggtgcg acacacaatc ctcatgggaa caggatcacc catgcgctgc 180
ccttgatgat caaggttggg gcttaagtgg attaagggag gcaagttctg ggttccttgc 240
cttttcaaac catgaagtca ggctctgtat ccctcctttt cctaactgat attctaacta 300
a 301

<210> 248
<211> 301
<212> DNA
<213> Homo sapien

<400> 248
aggtccttgg agatgccatt tcagccgaag gactcttctw ttcggaagta caccctcact 60
attaggaaga ttcttagggg taatttttct gaggaaggag aactagccaa cttaagaatt 120

acaggaagaa agtggtttgg aagacagcca aagaaataaa agcagattaa attgtatcag 180
gtacattcca gcctgttggc aactccataa aaacatttca gattttaatc ccgaatttag 240
ctaatgagac tggatttttg tttttatgt tgtgtgtcgc agagctaaaa actcagttcc 300
c 301

<210> 249
<211> 301
<212> DNA
<213> Homo sapien

<400> 249
gtccagagga agcacctggt gctgaactag gcttgccctg ctgtgaactt gcacttggag 60
ccctgacgct gctgttctcc ccgaaaaacc cgaccgacct ccgcgatctc cgtcccgccc 120
ccagggagac acagcagtga ctcagagctg gtcgcacact gtgcctccct cctcaccgcc 180
catcgtaatg aattattttg aaaattaatt ccaccatcct ttcagattct ggatggaaag 240
actgaatctt tgactcagaa ttgtttgctg aaaagaatga tgtgactttc ttagtcattt 300
a 301

<210> 250
<211> 301
<212> DNA
<213> Homo sapien

<400> 250
ggtctgtgac aaggacttgc aggctgtggg aggcaagtga cccttaacac tacacttctc 60
cttatcttta ttggcttgat aaacataatt atttctaaca ctagcttatt tccagttgcc 120
cataagcaca tcagtacttt tctctggctg gaatagtaaa ctaaagtatg gtacatctac 180
ctaaaagact actatgtgga ataatacata ctaatgaagt attacatgat ttaaagacta 240
caataaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat gattgaaacc 300
a 301

<210> 251
<211> 301
<212> DNA
<213> Homo sapien

<400> 251
gccgaggtcc tacatttggc ccagtttccc cctgcatcct ctccagggcc cctgcctcat 60
agacaacctc atagagcata ggagaactgg ttgccctggg ggcagggga ctgtctggat 120
ggcaggggtc ctcaaaaatg ccactgtcac tgccaggaaa tgcttctgag cagtacacct 180
cattgggatc aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggcccggaa 240
cctctggagg ggggcagtgg aatcccagct ccaggacgga tcctgtcgaa aagatatcct 300
c 301

<210> 252
<211> 301
<212> DNA
<213> Homo sapien

<400> 252
gcaaccaatc actctgtttc acgtgacttt tatcaccata caatttgtgg catttcctca 60
ttttctacat tgtagaatca agagtgtaaa taaatgtata tcgatgtctt caagaatata 120
tcattccttt ttcactagga acccattcaa aatataagtc aagaatctta atatcaacaa 180
atatatcaag caaactggaa ggcagaataa ctaccataat ttagtataag tacccaaagt 240
tttataaatc aaaagcccta atgataacca tttttagaat tcaatcatca ctgtagaatc 300
a 301

<210> 253

<211> 301
<212> DNA
<213> Homo sapien

<400> 253
ttccctaaga agatgttatt ttgttgggtt ttgttccccc tccatctcga ttctcgtacc 60
caactaaaaa aaaaaaataa agaaaaaatg tgctgcgttc tgaaaaataa ctccttagct 120
tggtctgatt gttttcagac cttaaaatat aaacttgttt cacaagcttt aatccatgtg 180
gatttttttt cttagagaac cacaaaacat aaaaggagca agtcggactg aatacctgtt 240
tccatagtgc ccacagggta ttcctcacat tttctccata ggaaaatgct ttttcccaag 300
g 301

<210> 254
<211> 301
<212> DNA
<213> Homo sapien

<400> 254
cgctgcgcct ttcccttggg ggaggggcaa ggccagaggg ggtccaagtg cagcacgagg 60
aacttgacca attcccttga agcgggtggg ttaaaccctg taaatgggaa caaaatcccc 120
ccaaatctct tcatcttacc ctggtggact cctgactgta gaatttttg gttgaaacaa 180
gaaaaaaata aagctttgga cttttcaagg ttgcttaaca ggtactgaaa gactggcctc 240
acttaaactg agccaggaaa agctgcagat ttattaatgg gtgtgttagt gtgcagtgcc 300
t 301

<210> 255
<211> 302
<212> DNA
<213> Homo sapien

<400> 255
agcttttttt tttttttttt tttttttttt ttcattaaaa aatagtgctc tttattataa 60
attactgaaa tgtttctttt ctgaatataa atataaatat gtgcaaagtt tgacttggat 120
tgggattttg ttgagttctt caagcatctc ctaataccct caagggcctg agtagggggg 180
aggaaaaagg actggaggtg gaatctttat aaaaaacaag agtgattgag gcagattgta 240
aacattatta aaaaacaaga aacaaacaaa aaaatagaga aaaaaaccac cccaacacac 300
aa 302

<210> 256
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 256
gttccagaaa acattgaagg tggcttccca aagtctaact agggataccc cctctagcct 60
aggaccctcc tccccacacc tcaatccacc aaaccatcca taatgcaccc agataggccc 120
acccccaaaa gcctggacac cttgagcaca cagttatgac caggacagac tcatctctat 180
aggcaaatag ctgctggcaa actggcatta cctggtttgt ggggatgggg gggcaagtgt 240
gtggcctctc ggcctggtta gcaagaacat tcagggtagg cctaagttan tcgtgttagt 300
t 301

<210> 257
<211> 301

<212> DNA
<213> Homo sapien

<400> 257
gttgtggagg aactctggct tgctcattaa gtcctactga ttttcactat cccctgaatt 60
tccccactta tttttgtctt tcactatcgc aggccttaga agaggtctac ctgcctccag 120
tcttacctag tccagtctac cccctggagt tagaatggcc atcctgaagt gaaaagtaat 180
gtcacattac tcccttcagt gatttcttgt agaagtgcca atccctgaat gccaccaaga 240
tcttaatctt cacatcttta atcttatctc tttgactcct ctttacaccg gagaaggctc 300
c 301

<210> 258
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 258
cagcagtagt agatgccgta tgccagcacg cccagcactc ccaggatcag caccagcacc 60
aggggcccag ccaccaggcg cagaagcaag ataaacagta ggctcaagac cagagccacc 120
cccagggcaa caagaatcca ataccaggac tgggcaaaat cttcaaagat cttaacactg 180
atgtctcggg cattgaggct gtcaataana cgctgatccc ctgctgtatg gtggtgtcat 240
tggtgatccc tgggagcgcc ggtggagtaa cgttggtcca tggaaagcag cgcccacaac 300
t 301

<210> 259
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 259
tcatatatgc aaacaaatgc agactangcc tcaggcagag actaaaggac atctcttggg 60
gtgtcctgaa gtgatttgga cccctgaggg cagacaccta agtaggaatc ccagtgggaa 120
gcaaagccat aaggaagccc aggattcctt gtgatcagga agtgggccag gaaggtctgt 180
tccagctcac atctcatctg catgcagcac ggaccggatg cgcccactgg gtcttggctt 240
ccctcccatc ttctcaagca gtgtccttgt tgagccattt gcatccttgg ctccaggtgg 300
c 301

<210> 260
<211> 301
<212> DNA
<213> Homo sapien

<400> 260
ttttttttct ccctaaggaa aaagaaggaa caagtctcat aaaaccaaat aagcaatggt 60
aaggtgtctt aacttgaaaa agattaggag tcactggttt acaagttata attgaatgaa 120
agaactgtaa cagccacagt tggccatttc atgccaatgg cagcaaacaa caggattaac 180
tagggcaaaa taaataagtg tgtggaagcc ctgataagtg cttaataaac agactgattc 240
actgagacat cagtacctgc ccgggcggcc gctcgagccg aattctgcag atatccatca 300

c 301

<210> 261
<211> 301
<212> DNA
<213> Homo sapien

<400> 261
aaatattcga gcaaatcctg taactaatgt gtctccataa aaggctttga actcagtgaa 60
tctgcttcca tccacgattc tagcaatgac ctctcggaca tcaaagctcc tcttaaggtt 120
agcaccaact attccataca attcatcagc aggaaataaa ggctcttcag aaggttcaat 180
ggtgacatcc aatttcttct gataatttag attcctcaca accttcctag ttaagtgaag 240
ggcatgatga tcatccaaag cccagtggtc acttactcca gactttctgc aatgaagatc 300
a 301

<210> 262
<211> 301
<212> DNA
<213> Homo sapien

<400> 262
gaggagagcc tgttacagca tttgtaagca cagaatactc caggagtatt tgtaattgtc 60
tgtgagcttc ttgccgcaag tctctcagaa atttaaaaag atgcaaatcc ctgagtcacc 120
cctagacttc ctaaaccaga tcctctgggg ctggaacctg gcactctgca tttgtaatga 180
gggctttctg gtgcacacct aattttgtgc atctttgccc taaatcctgg attagtgccc 240
catcattacc cccacattat aatgggatag attcagagca gatactctcc agcaaagaat 300
c 301

<210> 263
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 263
tttagcttgt ggtaaatgac tcacaaaact gattttaaaa tcaagttaat gtgaattttg 60
aaaattacta cttaatccta attcacaata acaatggcat taaggtttga cttgagttgg 120
ttcttagtat tatttatggt aaataggctc ttaccacttg caaataactg gccacatcat 180
taatgactga cttcccagta aggctctcta aggggtaagt angaggatcc acaggatttg 240
agatgctaag gccccagaga tcgtttgatc caaccctctt attttcagag gggaaaatgg 300
g 301

<210> 264
<211> 301
<212> DNA
<213> Homo sapien

<400> 264
aaagacgtta aaccactcta ctaccacttg tggaactctc aaagggtaaa tgacaaascc 60
aatgaatgac tctaaaaaca atatttacat ttaatggttt gtagacaata aaaaaacaag 120
gtggatagat ctagaattgt aacattttaa gaaaaccata scatttgaca gatgagaaag 180
ctcaattata gatgcaaagt tataactaaa ctactatagt agtaaagaaa tacatttcac 240
acccttcata taaattcact atcttggctt gaggcactcc ataaaatgta tcacgtgcat 300
a 301

<210> 265
<211> 301
<212> DNA
<213> Homo sapien

<400> 265
tgcccaagtt atgtgtaagt gtatccgcac ccagaggtaa aactacactg tcatctttgt 60
cttcttgtga cgcagtattt cttctctggg gagaagccgg gaagtcttct cctggctcta 120
catattcttg gaagtctcta atcaactttt gttccatttg tttcatttct tcaggaggga 180
ttttcagttt gtcaacatgt tctctaacaa cacttgccca tttctgtaaa gaatccaaag 240
cagtccaagg ctttgacatg tcaacaacca gcataactag agtatccttc agagatacgg 300
c 301

<210> 266
<211> 301
<212> DNA
<213> Homo sapien

<400> 266
taccgtctgc ccttcctccc atccaggcca tctgcgaatc tacatgggtc ctcctattcg 60
acaccagatc actctttcct ctacccacag gcttgctatg agcaagagac acaacctcct 120
ctcttctgtg ttccagcttc ttttcctgtt cttcccaccc cttaagttct attcctgggg 180
atagagacac caatacccat aacctctctc ctaagcctcc ttataaccca gggtgcacag 240
cacagactcc tgacaactgg taaggccaat gaactgggag ctcacagctg gctgtgcctg 300
a 301

<210> 267
<211> 301
<212> DNA
<213> Homo sapien

<400> 267
aaagagcaca ggccagctca gcctgccctg gccatctaga ctcagcctgg ctccatgggg 60
gttctcagtg ctgagtccat ccaggaaaag ctcacctaga ccttctgagg ctgaatcttc 120
atcctcacag gcagcttctg agagcctgat attcctagcc ttgatggtct ggagtaaagc 180
ctcattctga ttcctctcct tcttttcttt caagttggct ttcctcacat ccctctgttc 240
aattcgcttc agcttgtctg ctttagccct catttccaga agcttcttct ctttggcatc 300
t 301

<210> 268
<211> 301
<212> DNA
<213> Homo sapien

<400> 268
aatgtctcac tcaactactt cccagcctac cgtggcctaa ttctgggagt tttcttctta 60
gatcttggga gagctggttc ttctaaggag aaggaggaag gacagatgta actttggatc 120
tcgaagagga agtctaatgg aagtaattag tcaacggtcc ttgtttagac tcttggaata 180
tgctgggtgg ctcagtgagc ccttttggag aaagcaagta ttattcttaa ggagtaacca 240
cttcccattg ttctactttc taccatcatc aattgtatat tatgtattct ttggagaact 300
a 301

<210> 269
<211> 301
<212> DNA
<213> Homo sapien

<400> 269
taacaatata cactagctat ctttttaact gtccatcatt agcaccaatg aagattcaat 60
aaaattacct ttattcacac atctcaaaac aattctgcaa attcttagtg aagtttaact 120
atagtcacag accttaaata ttcacattgt tttctatgtc tactgaaaat aagttcacta 180
cttttctgga tattctttac aaaatcttat taaaattcct ggtattatca cccccaatta 240
tacagtagca caaccacctt atgtagtttt tacatgatag ctctgtagaa gtttcacatc 300
t 301

<210> 270
<211> 301
<212> DNA
<213> Homo sapien

<400> 270
cattgaagag cttttgcgaa acatcagaac acaagtgctt ataaaattaa ttaagcctta 60
cacaagaata catattcctt ttatttctaa ggagttaaac atagatgtag ctgatgtgga 120
gagcttgctg gtgcagtgca tattggataa cactattcat ggccgaattg atcaagtcaa 180
ccaactcctt gaactggatc atcagaagaa gggtggtgca cgatatactg cactagataa 240
tggaccaacc aactaaattc tctcaccagg ctgtatcagt aaactggctt aacagaaaac 300
a 301

<210> 271
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 271
aaaaggttct cataagatta acaatttaaa taaatatttg atagaacatt ctttctcatt 60
tttatagctc atctttaggg ttgatattca gttcatgctt cccttgctgt tcttgatcca 120
gaattgcaat cacttcatca gcctgtattc gctccaattc tctataaagt gggtccaagg 180
tgaaccacag agccacagca cacctctttc ccttggtgac tgccttcacc ccatganggt 240
tctctcctcc agatganaac tgatcatgcg cccacatttt gggttttata gaagcagtca 300
c 301

<210> 272
<211> 301
<212> DNA
<213> Homo sapien

<400> 272
taaattgcta agccacagat aacaccaatc aaatggaaca aatcactgtc ttcaaatgtc 60
ttatcagaaa accaaatgag cctggaatct tcataatacc taaacatgcc gtatttagga 120
tccaataatt ccctcatgat gagcaagaaa aattctttgc gcacccctcc tgcatccaca 180
gcatcttctc caacaaatat aaccttgagt ggcttcttgt aatctatgtt ctttgttttc 240
ctaaggactt ccattgcatc tcctacaata ttttctctac gcaccactag aattaagcag 300
g 301

<210> 273
<211> 301
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 273
acatgtgtgt atgtgtatct ttgggaaaan aanaagacat cttgtttayt attttttttgg 60
agagangctg ggacatggat aatcacwtaa tttgctayta tyactttaat ctgactygaa 120
gaaccgtcta aaaataaaat ttaccatgtc dtatattcct tatagtatgc ttatttcacc 180
ttytttctgt ccagagagag tatcagtgac ananatttma gggtgaamac atgmattggt 240
gggacttnty tttacngagm accctgcccg sgcgccctcg makcngantt ccgcsananc 300
t 301

<210> 274
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 274
cttatatact ctttctcaga ggcaaaagag gagatgggta atgtagacaa ttctttgagg 60
aacagtaaat gattattaga gagaangaat ggaccaagga gacagaaatt aacttgtaaa 120
tgattctctt tggaatctga atgagatcaa gaggccagct ttagcttgtg gaaaagtcca 180
tctaggtatg gttgcattct cgtcttcttt tctgcagtag ataatgaggt aaccgaaggc 240
aattgtgctt cttttgataa gaagctttct tggtcatatc aggaaattcc aganaaagtc 300
c 301

<210> 275
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 275
tcggtgtcag cagcacgtgg cattgaacat tgcaatgtgg agcccaaacc acagaaaatg 60
gggtgaaatt ggccaacttt ctattaactt atgttggcaa ttttgccacc aacagtaagc 120
tggcccttct aataaaagaa aattgaaagg tttctcacta aacggaatta agtagtggag 180
tcaagagact cccaggcctc agcgtacctg cccgggcggc cgctcgaagc cgaattctgc 240
agatatccat cacactggcg gncgctcgan catgcatcta gaaggnccaa ttcgccctat 300
a 301

<210> 276
<211> 301
<212> DNA
<213> Homo sapien

<400> 276
tgtacacata ctcaataaat aaatgactgc attgtggtat tattactata ctgattatat 60
ttatcatgtg acttctaatt agaaaatgta tccaaaagca aaacagcaga tatacaaaat 120
taaagagaca gaagatagac attaacagat aaggcaactt atacattgag aatccaaatc 180
caatacattt aaacatttgg gaaatgaggg ggacaaatgg aagccagatc aaatttgtgt 240

aaaactattc agtatgtttc ccttgcttca tgtctgagaa ggctctcctt caatggggat 300
g 301

<210> 277
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 277
tttgttgatg tcagtatttt attacttgcg ttatgagtgc tcacctggga aattctaaag 60
atacagagga cttggaggaa gcagagcaac tgaatttaat ttaaaagaag gaaaacattg 120
gaatcatggc actcctgata ctttcccaaa tcaacactct caatgcccca ccctcgtcct 180
caccatagtg gggagactaa agtggccacg gatttgcctt angtgtgcag tgcgttctga 240
gttcnctgtc gattacatct gaccagtctc ctttttccga agtccntccg ttcaatcttg 300
c 301

<210> 278
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 278
taccactaca ctccagcctg ggcaacagag caagacctgt ctcaaagcat aaaatggaat 60
aacatatcaa atgaaacagg gaaaatgaag ctgacaattt atggaagcca gggcttgtca 120
cagtctctac tgttattatg cattacctgg gaatttatat aagcccttaa taataatgcc 180
aatgaacatc tcatgtgtgc tcacaatgtt ctggcactat tataagtgct tcacaggttt 240
tatgtgttct tcgtaacttt atggantagg tactcggccg cgaacacgct aagccgaatt 300
c 301

<210> 279
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 279
aaagcaggaa tgacaaagct tgcttttctg gtatgttcta ggtgtattgt gacttttact 60
gttatattaa ttgccaatat aagtaaatat agattatata tgtatagtgt ttcacaaagc 120
ttagaccttt accttccagc caccccacag tgcttgatat ttcagagtca gtcattggtt 180
atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac 240
catctgtttt cacatgaaat gccacacaca tagaactcca acatcaattt cattgcacag 300
a 301

<210> 280

<211> 301
<212> DNA
<213> Homo sapien

<400> 280
ggtactggag ttttcctccc ctgtgaaaac gtaactactg ttgggagtga attgaggatg 60
tagaaaggtg gtggaaccaa attgtggtca atggaaatag gagaatatgg ttctcactct 120
tgagaaaaaa acctaagatt agcccaggta gttgcctgta acttcagttt ttctgcctgg 180
gtttgatata gtttagggtt ggggttagat taagatctaa attacatcag gacaaagaga 240
cagactatta actccacagt taattaagga ggtatgttcc atgtttattt gttaaagcag 300
t 301

<210> 281
<211> 301
<212> DNA
<213> Homo sapien

<400> 281
aggtacaaga aggggaatgg gaaagagctg ctgctgtggc attgttcaac ttggatattc 60
gccgagcaat ccaaatcctg aatgaagggg catcttctga aaaaggagat ctgaatctca 120
atgtggtagc aatggcttta tcgggttata cggatgagaa gaactccctt tggagagaaa 180
tgtgtagcac actgcgatta cagctaaata acccgtattt gtgtgtcatg tttgcatttc 240
tgacaagtga aacaggatct tacgatggag ttttgtatga aaacaaagtt gcagtacctc 300
g 301

<210> 282
<211> 301
<212> DNA
<213> Homo sapien

<400> 282
caggtactac agaattaaaa tactgacaag caagtagttt cttggcgtgc acgaattgca 60
tccagaaccc aaaaattaag aaattcaaaa agacattttg tgggcacctg ctagcacaga 120
agcgcagaag caaagcccag gcagaaccat gctaacctta cagctcagcc tgcacagaag 180
cgcagaagca aagcccaggc agaaccatgc taaccttaca gctcagcctg cacagaagcg 240
cagaagcaaa gcccaggcag aacatgctaa ccttacagct cagcctgcac agaagcacag 300
a 301

<210> 283
<211> 301
<212> DNA
<213> Homo sapien

<400> 283
atctgtatac ggcagacaaa ctttatarag tgtagagagg tgagcgaaag gatgcaaaag 60
cactttgagg gctttataat aatatgctgc ttgaaaaaaa aaatgtgtag ttgatactca 120
gtgcatctcc agacatagta aggggttgct ctgaccaatc aggtgatcat tttttctatc 180
acttcccagg ttttatgcaa aaattttgtt aaattctata atggtgatat gcatctttta 240
ggaaacatat acatttttaa aaatctattt tatgtaagaa ctgacagacg aatttgcttt 300
g 301

<210> 284
<211> 301
<212> DNA
<213> Homo sapien

<400> 284
caggtacaaa acgctattaa gtggcttaga atttgaacat ttgtggtctt tatttacttt 60

gcttcgtgtg tgggcaaagc aacatcttcc ctaaatatat attaccaaga aaagcaagaa 120
gcagattagg tttttgacaa aacaaacagg ccaaaagggg gctgacctgg agcagagcat 180
ggtgagaggc aaggcatgag agggcaagtt tgttgtggac agatctgtgc ctactttatt 240
actggagtaa aagaaaacaa agttcattga tgtcgaagga tatatacagt gttagaaatt 300
a 301

<210> 285
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 285
acatcaccat gatcggatcc cccacccatt atacgttgta tgtttacata aatactcttc 60
aatgatcatt agtgttttaa aaaaaatact gaaaactcct tctgcatccc aatctctaac 120
caggaaagca aatgctattt acagacctgc aagccctccc tcaaacnaaa ctatttctgg 180
attaaatatg tctgacttct tttgaggtca cacgactagg caaatgctat ttacgatctg 240
caaaagctgt ttgaagagtc aaagcccccca tgtgaacacg atttctggac cctgtaacag 300
t 301

<210> 286
<211> 301
<212> DNA
<213> Homo sapien

<400> 286
taccactgca ttccagcctg ggtgacagag tgagactccg tctccaaaaa aaactttgct 60
tgtatattat ttttgcctta cagtggatca ttctagtagg aaaggacagt aagatttttt 120
atcaaaatgt gtcatgccag taagagatgt tatattcttt tctcatttct tccccaccca 180
aaaataagct accatatagc ttataagtct caaatttttg ccttttacta aaatgtgatt 240
gtttctgttc attgtgtatg cttcatcacc tatattaggc aaattccatt ttttcccttg 300
t 301

<210> 287
<211> 301
<212> DNA
<213> Homo sapien

<400> 287
tacagatctg ggaactaaat attaaaaatg agtgtggctg gatatatgga gaatgttggg 60
cccagaagga acgtagagat cagatattac aacagctttg ttttgagggt tagaaatatg 120
aaatgatttg gttatgaacg cacagtttag gcagcagggc cagaatcctg accctctgcc 180
ccgtggttat ctcctcccca gcttggctgc ctcatgttat cacagtattc cattttgttt 240
gttgcatgtc ttgtgaagcc atcaagattt tctcgtctgt tttcctctca ttggtaatgc 300
t 301

<210> 288
<211> 301
<212> DNA
<213> Homo sapien

<400> 288
gtacacctaa ctgcaaggac agctgaggaa tgtaatgggc agccgctttt aaagaagtag 60
agtcaatagg aagacaaatt ccagttccag ctcagtctgg gtatctgcaa agctgcaaaa 120

```
gatctttaaa gacaatttca agagaatatt tccttaaagt tggcaatttg gagatcatac     180
aaaagcatct gcttttgtga tttaatttag ctcatctggc cactggaaga atccaaacag     240
tctgccttaa ttttggatga atgcatgatg gaaattcaat aatttagaaa gttaaaaaaa     300
a                                                                     301

      <210> 289
      <211> 301
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(301)
      <223> n = A,T,C or G

      <400> 289
ggtacactgt ttccatgtta tgtttctaca cattgctacc tcagtgctcc tggaaactta      60
gcttttgatg tctccaagta gtccaccttc atttaactct ttgaaactgt atcatctttg     120
ccaagtaaga gtggtggcct atttcagctg ctttgacaaa atgactggct cctgacttaa     180
cgttctataa atgaatgtgc tgaagcaaag tgcccatggt ggcggcgaan aagagaaaga     240
tgtgttttgt tttggactct ctgtggtccc ttccaatgct gtgggtttcc aaccagngga     300
a                                                                     301

      <210> 290
      <211> 301
      <212> DNA
      <213> Homo sapien

      <220>
      <221> misc_feature
      <222> (1)...(301)
      <223> n = A,T,C or G

      <400> 290
acactgagct cttcttgata aatatacaga atgcttggca tatacaagat tctatactac      60
tgactgatct gttcatttct ctcacagctc ttacccccaa aagcttttcc accctaagtg     120
ttctgacctc cttttctaat cacagtaggg atagaggcag anccacctac aatgaacatg     180
gagttctatc aagaggcaga aacagcacag aatcccagtt ttaccattcg ctagcagtgc     240
tgccttgaac aaaaacattt ctccatgtct cattttcttc atgcctcaag taacagtgag     300
a                                                                     301

      <210> 291
      <211> 301
      <212> DNA
      <213> Homo sapien

      <400> 291
caggtaccaa tttcttctat cctagaaaca tttcatttta tgttgttgaa acataacaac      60
tatatcagct agattttttt tctatgcttt acctgctatg gaaaatttga cacattctgc     120
tttactcttt tgtttatagg tgaatcacaa aatgtatttt tatgtattct gtagttcaat     180
agccatggct gtttacttca tttaatttat ttagcataaa gacattatga aaaggcctaa     240
acatgagctt cacttcccca ctaactaatt agcatctgtt atttcttaac cgtaatgcct     300
a                                                                     301

      <210> 292
      <211> 301
      <212> DNA
      <213> Homo sapien
```

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 292
```
acctttttagt agtaatgtct aataataaat aagaaatcaa ttttataagg tccatatagc      60
tgtattaaat aatttttaag tttaaaagat aaaataccat cattttaaat gttggtattc     120
aaaaccaaag natataaccg aaaggaaaaa cagatgagac ataaaatgat ttgcnagatg     180
ggaaatatag tasttyatga atgttnatta aattccagtt ataatagtgg ctacacactc     240
tcactacaca cacagacccc acagtcctat atgccacaaa cacatttcca taacttgaaa     300
a                                                                     301
```

<210> 293
<211> 301
<212> DNA
<213> Homo sapien

<400> 293
```
ggtaccaagt gctggtgcca gcctgttacc tgttctcact gaaaagtctg gctaatgctc      60
ttgtgtagtc acttctgatt ctgacaatca atcaatcaat ggcctagagc actgactgtt     120
aacacaaacg tcactagcaa agtagcaaca gctttaagtc taaatacaaa gctgttctgt     180
gtgagaattt tttaaaaggc tacttgtata ataacccttg tcatttttaa tgtacctcgg     240
ccgcgaccac gctaagccga attctgcaga tatccatcac actggcggcc gctcgagcat     300
g                                                                     301
```

<210> 294
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 294
```
tgacccataa caatatacac tagctatctt tttaactgtc catcattagc accaatgaag      60
attcaataaa attaccttta ttcacacatc tcaaaacaat tctgcaaatt cttagtgaag     120
tttaactata gtcacaganc ttaaatattc acattgtttt ctatgtctac tgaaaataag     180
ttcactactt ttctgggata ttctttacaa aatcttatta aaattcctgg tattatcacc     240
cccaattata cagtagcaca accaccttat gtagttttta catgatagct ctgtagaggt     300
t                                                                     301
```

<210> 295
<211> 305
<212> DNA
<213> Homo sapien

<400> 295
```
gtactctttc tctcccctcc tctgaattta attctttcaa cttgcaattt gcaaggatta      60
cacatttcac tgtgatgtat attgtgttgc aaaaaaaaaa gtgtctttgt ttaaaattac     120
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga     180
actggtagaa aaacrtctga agagctagtc tatcagcatc tgacaggtga attggatggt     240
tctcagaacc atttcaccca gacagcctgt ttctatcctg tttaataaat tagtttgggt     300
tctct                                                                 305
```

<210> 296
<211> 301
<212> DNA
<213> Homo sapien

<400> 296
aggtactatg ggaagctgct aaaataatat ttgatagtaa aagtatgtaa tgtgctatct 60
cacctagtag taaactaaaa ataaactgaa actttatgga atctgaagtt attttccttg 120
attaaataga attaataaac caatatgagg aaacatgaaa ccatgcaatc tactatcaac 180
tttgaaaaag tgattgaacg aaccacttag ctttcagatg atgaacactg ataagtcatt 240
tgtcattact ataaatttta aaatctgtta ataagatggc ctatagggag gaaaaagggg 300
c 301

<210> 297
<211> 300
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(300)
<223> n = A,T,C or G

<400> 297
actgagtttt aactggacgc caagcaggca aggctggaag gttttgctct ctttgtgcta 60
aaggttttga aaaccttgaa ggagaatcat tttgacaaga agtacttaag agtctagaga 120
acaaagangt gaaccagctg aaagctctcg gggaanctt acatgtgttg ttaggcctgt 180
tccatcattg ggagtgcact ggccatccct caaaatttgt ctgggctggc ctgagtggtc 240
accgcacctc ggccgcgacc acgctaagcc gaattctgca gatatccatc acactggcgg 300

<210> 298
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 298
tatggggttt gtcacccaaa agctgatgct gagaaaggcc tccctggggc cctcccgcg 60
ggcatctgag agacctggtg ttccagtgtt tctggaaatg ggtcccagtg ccgccggctg 120
tgaagctctc agatcaatca cgggaagggc ctggcggtgg tggccacctg gaaccaccct 180
gtcctgtctg tttacatttc actaycaggt tttctctggg cattacnatt tgttccccta 240
caacagtgac ctgtgcattc tgctgtggcc tgctgtgtct gcaggtggct ctcagcgagg 300
t 301

<210> 299
<211> 301
<212> DNA
<213> Homo sapien

<400> 299
gttttgagac ggagtttcac tcttgttgcc cagactggac tgcaatggca gggtctctgc 60
tcactgcacc ctctgcctcc caggttcgag caattctcct gcctcagcct cccaggtagc 120
tgggattgca ggctcacgcc accataccca gctaattttt ttgtattttt agtagagacg 180
gagtttcgcc atgttggcca gctggtctca aactcctgac ctcaagcgac ctgcctgcct 240

cggcctccca aagtgctgga attataggca tgagtcaaca cgcccagcct aaagatattt 300
t 301

<210> 300
<211> 301
<212> DNA
<213> Homo sapien

<400> 300
attcagtttt atttgctgcc ccagtatctg taaccaggag tgccacaaaa tcttgccaga 60
tatgtcccac acccactggg aaaggctccc acctggctac ttcctctatc agctgggtca 120
gctgcattcc acaaggttct cagcctaatg agtttcacta cctgccagtc tcaaaactta 180
gtaaagcaag accatgacat tcccccacgg aaatcagagt ttgccccacc gtcttgttac 240
tataaagcct gcctctaaca gtccttgctt cttcacacca atcccgagcg catcccccat 300
g 301

<210> 301
<211> 301
<212> DNA
<213> Homo sapien

<400> 301
ttaaattttt gagaggataa aaaggacaaa taatctagaa atgtgtcttc ttcagtctgc 60
agaggacccc aggtctccaa gcaaccacat ggtcaagggc atgaataatt aaaagttggt 120
gggaactcac aaagaccctc agagctgaga cacccacaac agtgggagct cacaaagacc 180
ctcagagctg agacacccac aacagtggga gctcacaaag accctcagag ctgagacacc 240
cacaacagca cctcgttcag ctgccacatg tgtgaataag gatgcaatgt ccagaagtgt 300
t 301

<210> 302
<211> 301
<212> DNA
<213> Homo sapien

<400> 302
aggtacacat ttagcttgtg gtaaatgact cacaaaactg attttaaaat caagttaatg 60
tgaattttga aaattactac ttaatcctaa ttcacaataa caatggcatt aaggtttgac 120
ttgagttggt tcttagtatt atttatggta aataggctct taccacttgc aaataactgg 180
ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca 240
caggatttga gatgctaagg ccccagagat cgtttgatcc aaccctctta ttttcagagg 300
g 301

<210> 303
<211> 301
<212> DNA
<213> Homo sapien

<400> 303
aggtaccaac tgtggaaata ggtagaggat catttttttct ttccatatca actaagttgt 60
atattgtttt ttgacagttt aacacatctt cttctgtcag agattctttc acaatagcac 120
tggctaatgg aactaccgct tgcatgttaa aaatggtggt ttgtgaaatg atcataggcc 180
agtaacgggt atgtttttct aactgatctt ttgctcgttc caaaggacc tcaagacttc 240
catcgatttt atatctgggg tctagaaaag gagttaatct gttttccctc ataaattcac 300
c 301

<210> 304
<211> 301
<212> DNA

<213> Homo sapien

<400> 304
acatggatgt tattttgcag actgtcaacc tgaatttgta tttgcttgac attgcctaat 60
tattagtttc agtttcagct tacccacttt ttgtctgcaa catgcaraas agacagtgcc 120
ctttttagtg tatcatatca ggaatcatct cacattggtt tgtgccatta ctggtgcagt 180
gactttcagc cacttgggta aggtggagtt ggccatatgt ctccactgca aaattactga 240
ttttcctttt gtaattaata agtgtgtgtg tgaagattct ttgagatgag gtatatatct 300
c 301

<210> 305
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 305
gangtacagc gtggtcaagg taacaagaag aaaaaaatgt gagtggcatc ctgggatgag 60
caggggggaca gacctggaca gacacgttgt catttgctgc tgtgggtagg aaaatgggcg 120
taaaggagga gaaacagata caaaatctcc aactcagtat taaggtattc tcatgcctag 180
aatattggta gaaacaagaa tacattcata tggcaaataa ctaaccatgg tggaacaaaa 240
ttctgggatt taagttggat accaangaaa ttgtattaaa agagctgttc atggaataag 300
a 301

<210> 306
<211> 8
<212> PRT
<213> Homo sapien

<400> 306
Val Leu Gly Trp Val Ala Glu Leu
1 5

<210> 307
<211> 637
<212> DNA
<213> Homo sapien

<400> 307
acagggratg aagggaaagg gagaggatga ggaagccccc ctggggattt ggtttggtcc 60
ttgtgatcag gtggtctatg gggcttatcc ctacaaagaa gaatccagaa ataggggcac 120
attgaggaat gatacttgag cccaaagagc attcaatcat tgttttattt gccttmtttt 180
cacaccattg gtgagggagg gattaccacc ctggggttat gaagatggtt gaacacccca 240
cacatagcac cggagatatg agatcaacag tttcttagcc atagagattc acagcccaga 300
gcaggaggac gcttgcacac catgcaggat gacatggggg atgcgctcgg gattggtgtg 360
aagaagcaag gactgttaga ggcaggcttt atagtaacaa gacggtgggg caaactctga 420
tttccgtggg ggaatgtcat ggtcttgctt tactaagttt tgagactggc aggtagtgaa 480
actcattagg ctgagaacct tgtggaatgc acttgaccca sctgatagag gaagtagcca 540
ggtgggagcc tttcccagtg ggtgtgggac atatctggca agatttgtg gcactcctgg 600
ttacagatac tggggcagca aataaaactg aatcttg 637

<210> 308
<211> 647
<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(647)
<223> n = A,T,C or G

<400> 308
acgattttca ttatcatgta aatcgggtca ctcaaggggc caaccacagc tgggagccac 60
tgctcagggg aaggttcata tgggactttc tactgcccaa ggttctatac aggatataaa 120
ggngcctcac agtatagatc tggtagcaaa gaagaagaaa caaacactga tctctttctg 180
ccacccctct gaccctttgg aactcctctg accctttaga acaagcctac ctaatatctg 240
ctagagaaaa gaccaacaac ggcctcaaag gatctcttac catgaaggtc tcagctaatt 300
cttggctaag atgtgggttc cacattaggt tctgaatatg gggggaaggg tcaatttgct 360
cattttgtgt gtggataaag tcaggatgcc caggggccag agcagggggc tgcttgcttt 420
gggaacaatg gctgagcata taaccatagg ttatggggaa caaaacaaca tcaaagtcac 480
tgtatcaatt gccatgaaga cttgagggac ctgaatctac cgattcatct taaggcagca 540
ggaccagttt gagtggcaac aatgcagcag cagaatcaat ggaaacaaca gaatgattgc 600
aatgtccttt tttttctcct gcttctgact tgataaaagg ggaccgt 647

<210> 309
<211> 460
<212> DNA
<213> Homo sapien

<400> 309
actttatagt ttaggctgga cattggaaaa aaaaaaaagc cagaacaaca tgtgatagat 60
aatatgattg gctgcacact tccagactga tgaatgatga acgtgatgga ctattgtatg 120
gagcacatct tcagcaagag ggggaaatac tcatcatttt tggccagcag ttgtttgatc 180
accaaacatc atgccagaat actcagcaaa ccttcttagc tcttgagaag tcaaagtccg 240
ggggaattta ttcctggcaa ttttaattgg actccttatg tgagagcagc ggctacccag 300
ctggggtggt ggagcgaacc cgtcactagt ggacatgcag tggcagagct cctggtaacc 360
acctagagga atacacaggc acatgtgtga tgccaagcgt gacacctgta gcactcaaat 420
ttgtcttgtt tttgtctttc ggtgtgtaag attcttaagt 460

<210> 310
<211> 539
<212> DNA
<213> Homo sapien

<400> 310
acgggactta tcaaataaag ataggaaaag aagaaaactc aaatattata ggcagaaatg 60
ctaaaggttt taaaatatgt caggattgga agaaggcatg gataaagaac aaagttcagt 120
taggaaagag aaacacagaa ggaagagaca caataaaagt cattatgtat tctgtgagaa 180
gtcagacagt aagatttgtg ggaaatgggt tggtttgttg tatggtatgt attttagcaa 240
taatctttat ggcagagaaa gctaaaatcc tttagcttgc gtgaatgatc acttgctgaa 300
ttcctcaagg taggcatgat gaaggagggt ttagaggaga cacagacaca atgaactgac 360
ctagatagaa agccttagta tactcagcta ggaatagtga ttctgagggc acactgtgac 420
atgattatgt cattacatgt atggtagtga tggggatgat aggaaggaag aacttatggc 480
atattttcac ccccacaaaa gtcagttaaa tattgggaca ctaaccatcc aggtcaaga 539

<210> 311
<211> 526
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(526)
<223> n = A,T,C or G

<400> 311
caaatttgag ccaatgacat agaattttac aaatcaagaa gcttattctg gggccatttc 60
ttttgacgtt ttctctaaac tactaaagag gcattaatga tccataaatt atattatcta 120
catttacagc atttaaaatg tgttcagcat gaaatattag ctacagggga agctaaataa 180
attaaacatg gaataaagat ttgtccttaa atataatcta caagaagact ttgatatttg 240
tttttcacaa gtgaagcatt cttataaagt gtcataacct ttttggggaa actatgggaa 300
aaaatgggga aactctgaag ggttttaagt atcttacctg aagctacaga ctccataacc 360
tctctttaca gggagctcct gcagccccta cagaaatgag tggctgagat tcttgattgc 420
acagcaagag cttctcatct aaaccctttc cctttttagt atctgtgtat caagtataaa 480
agttctataa actgtagtnt acttatttta atccccaaag cacagt 526

<210> 312
<211> 500
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(500)
<223> n = A,T,C or G

<400> 312
cctctctctc cccacccccct gactctagag aactgggttt tctcccagta ctccagcaat 60
tcatttctga aagcagttga gccactttat tccaaagtac actgcagatg ttcaaactct 120
ccatttctct ttcccttcca cctgccagtt ttgctgactc tcaacttgtc atgagtgtaa 180
gcattaagga cattatgctt cttcgattct gaagacaggc cctgctcatg gatgactctg 240
gcttcttagg aaaatatttt tcttccaaaa tcagtaggaa atctaaactt atcccctctt 300
tgcagatgtc tagcagcttc agacatttgg ttaagaaccc atgggaaaaa aaaaaatcct 360
tgctaatgtg gtttcctttg taaaccanga ttcttatttg nctggtatag aatatcagct 420
ctgaacgtgt ggtaaagatt tttgtgtttg aatataggag aaatcagttt gctgaaaagt 480
tagtcttaat tatctattgg 500

<210> 313
<211> 718
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(718)
<223> n = A,T,C or G

<400> 313
ggagatttgt gtggtttgca gccgagggag accaggaaga tctgcatggt gggaaggacc 60
tgatgataca gaggtgagaa ataagaaagg ctgctgactt taccatctga ggccacacat 120
ctgctgaaat ggagataatt aacatcacta gaaacagcaa gatgacaata taatgtctaa 180
gtagtgacat gtttttgcac atttccagcc cttttaaata tccacacaca caggaagcac 240
aaaaggaagc acagagatcc ctgggagaaa tgcccggccg ccatcttggg tcatcgatga 300
gcctcgccct gtgcctgntc ccgcttgtga gggaaggaca ttagaaaatg aattgatgtg 360
ttccttaaag gatggcagga aaacagatcc tgttgtggat atttatttga acgggattac 420
agatttgaaa tgaagtcaca aagtgagcat taccaatgag aggaaaacag acgagaaaat 480
cttgatggtt cacaagacat gcaacaaaca aaatggaata ctgtgatgac acgagcagcc 540
aactggggag gagataccac ggggcagagg tcaggattct ggccctgctg cctaactgtg 600
cgttatacca atcatttcta tttctaccct caaacaagct gtngaatatc tgacttacgg 660
ttcttntggc ccacattttc atnatccacc ccntcntttt aannttantc caaantgt 718

<210> 314
<211> 358
<212> DNA
<213> Homo sapien

<400> 314
gtttatttac attacagaaa aaacatcaag acaatgtata ctatttcaaa tatatccata 60
cataatcaaa tatagctgta gtacatgttt tcattggtgt agattaccac aaatgcaagg 120
caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg tgtagtccaa 180
gctctcggta gtccagccac tgtgaaacat gctcccttta gattaacctc gtggacgctc 240
ttgttgtatt gctgaactgt agtgccctgt attttgcttc tgtctgtgaa ttctgttgct 300
tctggggcat ttccttgtga tgcagaggac caccacacag atgacagcaa tctgaatt 358

<210> 315
<211> 341
<212> DNA
<213> Homo sapien

<400> 315
taccacctcc ccgctggcac tgatgagccg catcaccatg gtcaccagca ccatgaaggc 60
ataggtgatg atgaggacat ggaatgggcc cccaaggatg gtctgtccaa agaagcgagt 120
gaccccccatt ctgaagatgt ctggaacctc taccagcagg atgatgatag ccccaatgac 180
agtcaccagc tccccgacca gccggatatc gtccttaggg gtcatgtagg cttcctgaag 240
tagcttctgc tgtaagaggg tgttgtcccg gggctcgtg cggttattgg tcctgggctt 300
gagggggcgg tagatgcagc acatggtgaa gcagatgatg t 341

<210> 316
<211> 151
<212> DNA
<213> Homo sapien

<400> 316
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tgtgggcctt tctcgagttt ctgattataa acaccactgg agcgatgtgt tgactggact 120
cattcaggga gctctggttg caatattagt t 151

<210> 317
<211> 151
<212> DNA
<213> Homo sapien

<400> 317
agaactagtg gatcctaatg aaatacctga aacatatatt ggcatttatc aatggctcaa 60
atcttcattt atctctggcc ttaaccctgg ctcctgaggc tgcggccagc agatcccagg 120
ccagggctct gttcttgcca cacctgcttg a 151

<210> 318
<211> 151
<212> DNA
<213> Homo sapien

<400> 318
actggtggga ggcgctgttt agttggctgt tttcagaggg gtctttcgga gggacctcct 60
gctgcaggct ggagtgtctt tattcctggc gggagaccgc acattccact gctgaggctg 120
tgggggcggt ttatcaggca gtgataaaca t 151

<210> 319

<211> 151
<212> DNA
<213> Homo sapien

<400> 319
aactagtgga tccagagcta taggtacagt gtgatctcag ctttgcaaac acattttcta 60
catagatagt actaggtatt aatagatatg taaagaaaga aatcacacca ttaataatgg 120
taagattggg tttatgtgat tttagtgggt a 151

<210> 320
<211> 150
<212> DNA
<213> Homo sapien

<400> 320
aactagtgga tccactagtc cagtgtggtg gaattccatt gtgttggggt tctagatcgc 60
gagcggctgc cctttttttt tttttttttg ggggggaatt tttttttttt aatagttatt 120
gagtgttcta cagcttacag taaataccat 150

<210> 321
<211> 151
<212> DNA
<213> Homo sapien

<400> 321
agcaactttg tttttcatcc aggttatttt aggcttagga tttcctctca cactgcagtt 60
tagggtggca ttgtaaccag ctatggcata ggtgttaacc aaaggctgag taaacatggg 120
tgcctctgag aaatcaaagt cttcatacac t 151

<210> 322
<211> 151
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(151)
<223> n = A,T,C or G

<400> 322
atccagcatc ttctcctgtt tcttgccttc ctttttcttc ttcttasatt ctgcttgagg 60
tttgggcttg gtcagtttgc cacagggctt ggagatggtg acagtcttct ggcattcggc 120
attgtgcagg gctcgcttca nacttccagt t 151

<210> 323
<211> 151
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(151)
<223> n = A,T,C or G

<400> 323
tgaggacttg tkttcttttt ctttattttt aatcctctta ckttgtaaat atattgccta 60
nagactcant tactacccag tttgtggttt twtgggagaa atgtaactgg acagttagct 120
gttcaatyaa aaagacactt ancccatgtg g 151

<210> 324
<211> 461
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(461)
<223> n = A,T,C or G

<400> 324
acctgtgtgg aatttcagct ttcctcatgc aaaaggattt tgtatccccg gcctacttga 60
agaagtggtc agctaaagga atccaggttg ttggttggac tgttaatacc tttgatgaaa 120
agagttacta cgaatcccat cttggttcca gctatatcac tgacagcatg gtagaagact 180
gcgaacctca cttctagact ttcacggtgg gacgaaacgg gttcagaaac tgccaggggc 240
ctcatacagg gatatcaaaa taccctttgt gctacccagg ccctggggaa tcaggtgact 300
cacacaaatg caatagttgg tcactgcatt tttacctgaa ccaaagctaa acccggtgtt 360
gccaccatgc accatggcat gccagagttc aacactgttg ctcttgaaaa ttgggtctga 420
aaaaacgcac aagagcccct gccctgccct agctgangca c 461

<210> 325
<211> 400
<212> DNA
<213> Homo sapien

<400> 325
acactgtttc catgttatgt ttctacacat tgctacctca gtgctcctgg aaacttagct 60
tttgatgtct ccaagtagtc caccttcatt taactctttg aaactgtatc atctttgcca 120
agtaagagtg gtggcctatt tcagctgctt tgacaaaatg actggctcct gacttaacgt 180
tctataaatg aatgtgctga agcaaagtgc ccatggtggc ggcgaagaag agaaagatgt 240
gttttgtttt ggactctctg tggtcccttc caatgctgtg ggtttccaac caggggaagg 300
gtccctttg cattgccaag tgccataacc atgagcacta cgctaccatg gttctgcctc 360
ctggccaagc aggctggttt gcaagaatga aatgaatgat 400

<210> 326
<211> 1215
<212> DNA
<213> Homo sapien

<400> 326
ggaggactgc agcccgcact cgcagccctg gcaggcggca ctggtcatgg aaaacgaatt 60
gttctgctcg ggcgtcctgg tgcatccgca gtgggtgctg tcagccgcac actgtttcca 120
gaactcctac accatcgggc tgggcctgca cagtcttgag gccgaccaag agccagggag 180
ccagatggtg gaggccagcc tctccgtacg gcacccagag tacaacagac ccttgctcgc 240
taacgacctc atgctcatca agttggacga atccgtgtcc gagtctgaca ccatccggag 300
catcagcatt gcttcgcagt gccctaccgc ggggaactct tgcctcgttt ctggctgggg 360
tctgctggcg aacggcagaa tgcctaccgt gctgcagtgc gtgaacgtgt cggtggtgtc 420
tgaggaggtc tgcagtaagc tctatgaccc gctgtaccac cccagcatgt tctgcgccgg 480
cggagggcaa gaccagaagg actcctgcaa cggtgactct gggggcccc tgatctgcaa 540
cgggtacttg cagggccttg tgtctttcgg aaaagccccg tgtggccaag ttggcgtgcc 600
aggtgtctac accaacctct gcaaattcac tgagtggata gagaaaaccg tccaggccag 660
ttaactctgg ggactgggaa cccatgaaat tgaccccaa atacatcctg cggaaggaat 720
tcaggaatat ctgttcccag cccctcctcc ctcaggccca ggagtccagg cccccagccc 780
ctcctccctc aaaccaaggg tacagatccc cagcccctcc tccctcagac ccaggagtcc 840
agaccccca gcccctcctc cctcagaccc aggagtccag cccctcctcc ctcagaccca 900
ggagtccaga ccccccagcc cctcctccct cagacccagg ggtccaggcc cccaacccct 960
cctccctcag actcagaggt ccaagccccc aacccctcct tccccagacc cagaggtcca 1020

ggtcccagcc cctcctccct cagacccagc ggtccaatgc cacctagact ctccctgtac 1080
acagtgcccc cttgtggcac gttgacccaa ccttaccagt tggtttttca ttttttgtcc 1140
ctttccccta gatccagaaa taaagtctaa gagaagcgca aaaaaaaaaa aaaaaaaaaa 1200
aaaaaaaaaa aaaaa 1215

<210> 327
<211> 220
<212> PRT
<213> Homo sapien

<400> 327
Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu Val Met
1 5 10 15
Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val
20 25 30
Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly
35 40 45
Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu
50 55 60
Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala
65 70 75 80
Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp
85 90 95
Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn
100 105 110
Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro
115 120 125
Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu Val Cys
130 135 140
Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly
145 150 155 160
Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro
165 170 175
Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala
180 185 190
Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys
195 200 205
Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
210 215 220

<210> 328
<211> 234
<212> DNA
<213> Homo sapien

<400> 328
cgctcgtctc tggtagctgc agccaaatca taaacggcga ggactgcagc ccgcactcgc 60
agccctggca ggcggcactg gtcatggaaa acgaattgtt ctgctcgggc gtcctggtgc 120
atccgcagtg ggtgctgtca gccacacact gtttccagaa ctcctacacc atcgggctgg 180
gcctgcacag tcttgaggcc gaccaagagc cagggagcca gatggtggag gcca 234

<210> 329
<211> 77
<212> PRT
<213> Homo sapien

<400> 329
Leu Val Ser Gly Ser Cys Ser Gln Ile Ile Asn Gly Glu Asp Cys Ser

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1               5                   10                  15
Pro His Ser Gln Pro Trp Gln Ala Ala Leu Val Met Glu Asn Glu Leu
            20                  25                  30
Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Thr
        35                  40                  45
His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu
    50                  55                  60
Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala
65                  70                  75

      &lt;210&gt; 330
      &lt;211&gt; 70
      &lt;212&gt; DNA
      &lt;213&gt; Homo sapien

      &lt;400&gt; 330
cccaacacaa tggcccgatc ccatccctga ctccgccctc aggatcgctc gtctctggta      60
gctgcagcca                                                             70

      &lt;210&gt; 331
      &lt;211&gt; 22
      &lt;212&gt; PRT
      &lt;213&gt; Homo sapien

      &lt;400&gt; 331
Gln His Asn Gly Pro Ile Pro Ser Leu Thr Pro Pro Ser Gly Ser Leu
 1              5                   10                  15
Val Ser Gly Ser Cys Ser
            20

      &lt;210&gt; 332
      &lt;211&gt; 2507
      &lt;212&gt; DNA
      &lt;213&gt; Homo sapien

      &lt;400&gt; 332
tggtgccgct gcagccggca gagatggttg agctcatgtt cccgctgttg ctcctccttc      60
tgcccttcct tctgtatatg gctgcgcccc aaatcaggaa aatgctgtcc agtggggtgt     120
gtacatcaac tgttcagctt cctgggaaag tagttgtggt cacaggagct aatacaggta     180
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gcttcttagc tgaggaaaag cacctccacg ttttgatcaa caatgcagga gtgatgatgt     420
gtccgtactc gaagacagca gatggctttg agatgcacat aggagtcaac cacttgggtc     480
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taaatgtgtc ttccctcgca catcacctgg gaaggatcca cttccataac ctgcagggcg     600
agaaattcta caatgcaggc ctggcctact gtcacagcaa gctagccaac atcctcttca     660
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ctagagatat cataatagga taagaagacc ctcatatgac ctgcacagct cattttcctt    1260
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gaactagctt ctttgttcac aattcagttc ctcccaacca accagtcttc acttcaagag 1380
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cccaggcatg gtggatcacc ggaggtcagt agttcaagac cagcctggcc aacatggtga 1500
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cttttattgc acttgttttg accattaagc tatatgttta gaaatggtca ttttacggaa 2340
aaattagaaa aattctgata atagtgcaga ataaatgaat taatgtttta cttaatttat 2400
attgaactgt caatgacaaa taaaaattct ttttgattat tttttgtttt catttaccag 2460
aataaaaacg taagaattaa aagtttgatt acaaaaaaaa aaaaaaa 2507

<210> 333
<211> 3030
<212> DNA
<213> Homo sapien

<400> 333
gcaggcgact tgcgagctgg gagcgattta aaacgctttg gattcccccg gcctgggtgg 60
ggagagcgag ctgggtgccc cctagattcc ccgccccccgc acctcatgag ccgaccctcg 120
gctccatgga gcccggcaat tatgccacct tggatggagc caaggatatc gaaggcttgc 180
tgggagcggg aggggggcgg aatctggtcg cccactcccc tctgaccagc cacccagcgg 240
cgcctacgct gatgcctgct gtcaactatg ccccccttgga tctgccaggc tcggcggagc 300
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cttatggtta ctttggaggc gggtactact cctgccgagt gtcccggagc tcgctgaaac 420
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agtaccccag ycgcccccact gagtttgcct tctatccggg atatccggga acctaccagc 540
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gacatgactc cctgttgcct gtggacagtt accagtcttg ggctctcgct ggtggctgga 660
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<211> 2417
<212> DNA
<213> Homo sapien

<400> 334
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<211> 2984
<212> DNA
<213> Homo sapien

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      <211> 147
      <212> PRT
      <213> Homo sapien

      <400> 336
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Leu Asp Ser Glu Asn Thr Ser Gly Ala Leu Pro Arg Leu Pro Gln Thr
            20                  25                  30
Pro Lys Gln Pro Gln Lys Arg Ser Arg Ala Ala Phe Ser His Thr Gln
        35                  40                  45
Val Ile Glu Leu Glu Arg Lys Phe Ser His Gln Lys Tyr Leu Ser Ala
    50                  55                  60
Pro Glu Arg Ala His Leu Ala Lys Asn Leu Lys Leu Thr Glu Thr Gln
65                  70                  75                  80
Val Lys Ile Trp Phe Gln Asn Arg Arg Tyr Lys Thr Lys Arg Lys Gln
                85                  90                  95
Leu Ser Ser Glu Leu Gly Asp Leu Glu Lys His Ser Ser Leu Pro Ala
            100                 105                 110
Leu Lys Glu Glu Ala Phe Ser Arg Ala Ser Leu Val Ser Val Tyr Asn
        115                 120                 125
Ser Tyr Pro Tyr Tyr Pro Tyr Leu Tyr Cys Val Gly Ser Trp Ser Pro
    130                 135                 140
Ala Phe Trp
145

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      <211> 9
      <212> PRT
      <213> Homo sapien

      <400> 337
Ala Leu Thr Gly Phe Thr Phe Ser Ala
 1               5

      <210> 338
      <211> 9
      <212> PRT
      <213> Homo sapien

      <400> 338
Leu Leu Ala Asn Asp Leu Met Leu Ile
 1               5


      <210> 339
      <211> 318
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<212> PRT
<213> Homo sapien

<400> 339
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            20   25   30
Cys Thr Ser Thr Val Gln Leu Pro Gly Lys Val Val Val Val Thr Gly
        35   40   45
Ala Asn Thr Gly Ile Gly Lys Glu Thr Ala Lys Glu Leu Ala Gln Arg
    50   55   60
Gly Ala Arg Val Tyr Leu Ala Cys Arg Asp Val Glu Lys Gly Glu Leu
65   70   75   80
Val Ala Lys Glu Ile Gln Thr Thr Thr Gly Asn Gln Gln Val Leu Val
                85   90   95
Arg Lys Leu Asp Leu Ser Asp Thr Lys Ser Ile Arg Ala Phe Ala Lys
            100   105   110
Gly Phe Leu Ala Glu Glu Lys His Leu His Val Leu Ile Asn Asn Ala
        115   120   125
Gly Val Met Met Cys Pro Tyr Ser Lys Thr Ala Asp Gly Phe Glu Met
    130   135   140
His Ile Gly Val Asn His Leu Gly His Phe Leu Leu Thr His Leu Leu
145   150   155   160
Leu Glu Lys Leu Lys Glu Ser Ala Pro Ser Arg Ile Val Asn Val Ser
                165   170   175
Ser Leu Ala His His Leu Gly Arg Ile His Phe His Asn Leu Gln Gly
            180   185   190
Glu Lys Phe Tyr Asn Ala Gly Leu Ala Tyr Cys His Ser Lys Leu Ala
        195   200   205
Asn Ile Leu Phe Thr Gln Glu Leu Ala Arg Arg Leu Lys Gly Ser Gly
    210   215   220
Val Thr Thr Tyr Ser Val His Pro Gly Thr Val Gln Ser Glu Leu Val
225   230   235   240
Arg His Ser Ser Phe Met Arg Trp Met Trp Trp Leu Phe Ser Phe Phe
                245   250   255
Ile Lys Thr Pro Gln Gln Gly Ala Gln Thr Ser Leu His Cys Ala Leu
            260   265   270
Thr Glu Gly Leu Glu Ile Leu Ser Gly Asn His Phe Ser Asp Cys His
        275   280   285
Val Ala Trp Val Ser Ala Gln Ala Arg Asn Glu Thr Ile Ala Arg Arg
    290   295   300
Leu Trp Asp Val Ser Cys Asp Leu Leu Gly Leu Pro Ile Asp
305   310   315

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<211> 483
<212> DNA
<213> Homo sapien

<400> 340
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ctg 483

<210> 341
<211> 344
<212> DNA
<213> Homo sapien

<400> 341
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tatttttact aaccattcta tttttataga aatagctgag agtttctaaa ccaactctct 120
gctgccttac aagtattaaa tattttactt ctttccataa agagtagctc aaaatatgca 180
attaatttaa taatttctga tgatggtttt atctgcagta atatgtatat catctattag 240
aatttactta atgaaaaact gaagagaaca aaatttgtaa ccactagcac ttaagtactc 300
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<210> 342
<211> 592
<212> DNA
<213> Homo sapien

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<211> 382
<212> DNA
<213> Homo sapien

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aaaccaccaa gctgaaaaaa aa 382

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<211> 536
<212> DNA
<213> Homo sapien

<400> 344
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<210> 345
<211> 251
<212> DNA
<213> Homo sapien

<400> 345
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<210> 346
<211> 282
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(282)
<223> n = A,T,C or G

<400> 346
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<210> 347
<211> 201
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(201)
<223> n = A,T,C or G

<400> 347
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tctgagactg actggaccca cccagaccca gggcaaagat acatgttacc atatcatctt 180
tataaagaat ttttttttgt c 201

<210> 348
<211> 251
<212> DNA
<213> Homo sapien

<400> 348
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gccctgcctc c 251

<210> 349
<211> 251
<212> DNA
<213> Homo sapien

<400> 349
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cagaagggtc tgaactctac gtgttaccag agaacataat gcaattcatg cattccactt 180
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actcctggtt t 251

<210> 350
<211> 908
<212> DNA
<213> Homo sapien

<400> 350
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cacctgtaaa tttgatgggg aatgtttaag aattggagac actgtgactt gcgtctgtca 240
gttcaagtgc aacaatgact atgtgcctgt gtgtggctcc aatggggaga gctaccagaa 300
tgagtgttac ctgcgacagg ctgcatgcaa acagcagagt gagatacttg tggtgtcaga 360
aggatcatgt gccacagtcc atgaaggctc tggagaaact agtcaaaagg agacatccac 420
ctgtgatatt tgccagtttg gtgcagaatg tgacgaagat gccgaggatg tctggtgtgt 480
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ttatgataat gcatgccaaa tcaaagaagc atcgtgtcag aaacaggaga aaattgaagt 600
catgtctttg ggtcgatgtc aagataacac aactacaact actaagtctg aagatgggca 660
ttatgcaaga acagattatg cagagaatgc taacaaatta gaagaaagtg ccagagaaca 720
ccacatacct tgtccggaac attacaatgg cttctgcatg catgggaagt gtgagcattc 780
tatcaatatg caggagccat cttgcaggtg tgatgctggt tatactggac aacactgtga 840
aaaaaaggac tacagtgttc tatacgttgt tcccggtcct gtacgatttc agtatgtctt 900
aatcgcag 908

<210> 351
<211> 472
<212> DNA
<213> Homo sapien

<400> 351
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cattaacttg attttaaaat cagwtttgyg agtcatttac cacaagctaa atgtgtacac 180
tatgataaaa acaaccattg tattcctgtt tttctaaaca gtcctaattt ctaacactgt 240
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gatctgtcca caacaaactt gccctctcat gccttgcctc tcaccatgct ctgctccagg 360
tcagccccct tttggcctgt ttgttttgtc aaaaacctaa tctgcttctt gcttttcttg 420
gtaatatata tttagggaag atgttgcttt gcccacacac gaagcaaagt aa 472

<210> 352
<211> 251
<212> DNA
<213> Homo sapien

<400> 352
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tgtggataag gccaggtcaa tggctgcaag catgcagaga aagaggtaca tcggagcgtg 120
caggctgcgt tccgtcctta cgatgaagac cacgatgcag tttccaaaca ttgccactac 180
atacatggaa aggaggggga agccaaccca gaaatgggct ttctctaatc ctgggatacc 240
aataagcaca a 251

<210> 353
<211> 436
<212> DNA
<213> Homo sapien

<400> 353
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cacattatgg tattattact atactgatta tatttatcat gtgacttcta attaraaaat 120
gtatccaaaa gcaaaacagc agatatacaa aattaaagag acagaagata gacattaaca 180
gataaggcaa cttatacatt gacaatccaa atccaataca tttaaacatt tgggaaatga 240
gggggacaaa tggaagccar atcaaatttg tgtaaaacta ttcagtatgt ttcccttgct 300
tcatgtctga raaggctctc ccttcaatgg ggatgacaaa ctccaaatgc cacacaaatg 360
ttaacagaat actagattca cactggaacg ggggtaaaga agaaattatt ttctataaaa 420
gggctcctaa tgtagt 436

<210> 354
<211> 854
<212> DNA
<213> Homo sapien

<400> 354
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atcagggacc accctttggg ttgatatttt gcttaatctg catcttttga gtaagatcat 180
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aggactttgt caggtgcctt gctaaaagcc agatgcgttc ggcacttcct tggtctgagg 300
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gtgagtgaaa gatccccatt ataggagcac ttgggagaga tcatataaaa gctgactctt 420
gagtacatgc agtaatgggg tagatgtgtg tggtgtgtct tcattcctgc aagggtgctt 480
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caatatggaa ggctctaatt tgcccatatt tgaaataata attcagcttt ttgtaataca 660
aaataacaaa ggattgagaa tcatggtgtc taatgtataa aagacccagg aaacataaat 720
atatcaactg cataaatgta aaatgcatgt gacccaagaa ggccccaaag tggcagacaa 780
cattgtaccc attttccctt ccaaaatgtg agcggcgggc ctgctgcttt caaggctgtc 840
acacgggatg tcag 854

<210> 355
<211> 676
<212> DNA
<213> Homo sapien

<400> 355
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atccacaagt catacctgga tgtcagcgaa gagggcacgg aggcagcagc agccactggg 180
gacagcatcg ctgtaaaaag cctaccaatg agagctcagt tcaaggcgaa ccaccccttc 240
ctgttcttta taaggcacac tcataccaac acgatcctat tctgtggcaa gcttgcctct 300
ccctaatcag atggggttga gtaaggctca gagttgcaga tgaggtgcag agacaatcct 360
gtgactttcc cacggccaaa aagctgttca cacctcacgc acctctgtgc ctcagtttgc 420

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attagatttt cttgacttgt atgtatctgt gagatcttga ataagtgacc tgacatctct 660
gcttaaagaa aaccag 676

<210> 356
<211> 574
<212> DNA
<213> Homo sapien

<400> 356
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caagcttccc atttgtagat ctcagtgcct atgagtatct gacacctgtt cctctcttca 180
gtctcttagg gaggcttaaa tctgtctcag gtgtgctaag agtgccagcc caaggkggtc 240
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gagttctttt cttgggcaac agataaccag acaggactct aatcgtgctc ttattcaaca 360
ttcttctgtc tctgcctaga ctggaataaa aagccaatct ctctcgtggc acagggaagg 420
agatacaagc tcgtttacat gtgatagatc taacaaaggc atctaccgaa gtctggtctg 480
gatagacggc acagggagct cttaggtcag cgctgctggt tggaggacat tcctgagtcc 540
agctttgcag cctttgtgca acagtacttt ccca 574

<210> 357
<211> 393
<212> DNA
<213> Homo sapien

<400> 357
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aagccacaac caaracttga ttttatcaac aaaaacccct aaatataaac ggsaaaaaag 180
atagatataa ttattccagt ttttttaaaa cttaaaarat attccattgc cgaattaara 240
araarataag tgttatatgg aaagaagggc attcaagcac actaaaraaa cctgaggkaa 300
gcataatctg tacaaaatta aactgtcctt tttggcattt taacaaattt gcaacgktct 360
tttttttctt tttctgtttt ttttttttt tac 393

<210> 358
<211> 630
<212> DNA
<213> Homo sapien

<400> 358
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gcatagagta gggaagctaa tccagcacag ggaggtcaca gagacatccc taaggaagtg 180
gagtttaaac tgagagaagc aagtgcttaa actgaaggat gtgttgaaga agaagggaga 240
gtagaacaat ttgggcagag ggaaccttat agaccctaag gtgggaaggt tcaaagaact 300
gaaagagagc tagaacagct ggagccgttc tccggtgtaa agaggagtca aagagataag 360
attaaagatg tgaagattaa gatcttggtg gcattcaggg attggcactt ctacaagaaa 420
tcactgaagg gagtaatgtg acattacttt tcacttcagg atggccattc taactccagg 480
gggtagactg gactaggtaa gactggaggc aggtagacct cttctaaggc ctgcgatagt 540
gaaagacaaa aataagtggg gaaattcagg ggatagtgaa aatcagtagg acttaatgag 600
caagccagag gttcctccac aacaaccagt 630

<210> 359
<211> 620
<212> DNA

<213> Homo sapien

<400> 359
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taattaaaaa atgctactaa tatagaaaat ttataatcag aaaaataaat attcagggag 120
ctcaccagaa gaataaagtg ctctgccagt tattaaagga ttactgctgg tgaattaaat 180
atggcattcc ccaagggaaa tagagagatt cttctggatt atgttcaata tttatttcac 240
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aatgtcattg acttatcaaa tactatcttg gcatataacc tatgaaggca aaactaaaca 540
aacaaaaagc tcacaccaaa caaaaccatc aacttatttt gtattctata acatacgaga 600
ctgtaaagat gtgacagtgt 620

<210> 360
<211> 431
<212> DNA
<213> Homo sapien

<400> 360
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tgatgaatga tgaacgtgat ggactattgt atggagcaca tcttcagcaa gagggggaaa 120
tactcatcat ttttggccag cagttgtttg atcaccaaac atcatgccag aatactcagc 180
aaaccttctt agctcttgag aagtcaaagt ccgggggaat ttattcctgg caattttaat 240
tggactcctt atgtgagagc agcggctacc cagctggggt ggtggagcga acccgtcact 300
agtggacatg cagtggcaga gctcctggta accacctaga ggaatacaca ggcacatgtg 360
tgatgccaag cgtgacacct gtagcactca aatttgtctt gtttttgtct ttcggtgtgt 420
agattcttag t 431

<210> 361
<211> 351
<212> DNA
<213> Homo sapien

<400> 361
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ttgggtcctc tggtctcttg ccaagtttcc cagccactcg agggagaaat atcgggaggt 180
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caatcctgga ttcaatgtct gaaacctcgc tctctgcctg ctggacttct gaggccgtca 300
ctgccactct gtcctccagc tctgacagct cctcatctgt ggtcctgttg t 351

<210> 362
<211> 463
<212> DNA
<213> Homo sapien

<400> 362
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tgtagatgag ccggctgaag atcttgcgca tgcgcggctt cagggcgaag ttcttggcgc 120
ccccggtcac agaaatgacc aggttgggtg ttttcaggtg ccagtgctgg gtcagcagct 180
cgtaaaggat ttccgcgtcc gtgtcgcagg acagacgtat atacttccct ttcttcccca 240
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agttccattt ctcactttgg ttgatctggg tgccttccat gtgctggctc tgggcatagc 360
cacacttgca cacattctcc ctgataagca cgatggtgtg gacaggaagg aaggatttca 420
ttgagcctgc ttatggaaac tggtattgtt agcttaaata gac 463

<210> 363
<211> 653
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(653)
<223> n = A,T,C or G

<400> 363
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ctcttggnga ttctgggtga catcttcatg aatggcaacc gtgccagwga ggctgtcctc 120
tgggaggcac tacgcaagat gggactgcgt cctggggtga gacatcctct ccttggagat 180
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ctgaggccga agcccgggct gaagcaagaa cccgcatggg aattggagat gaggctgtgt 480
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attttggaga tccntggtcc agaattccat ttaccttctg ggccagatac caccagaatg 600
cccgctccag attccctcag acctttgccg gtcccattat tggtcstggt ggt 653

<210> 364
<211> 401
<212> DNA
<213> Homo sapien

<400> 364
actagaggaa agacgttaaa ccactctact accacttgtg gaactctcaa agggtaaatg 60
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aaaacaaggt ggatagatct agaattgtaa cattttaaga aaaccatagc atttgacaga 180
tgagaaagct caattataga tgcaaagtta taactaaact actatagtag taaagaaata 240
catttcacac ccttcatata aattcactat cttggcttga ggcactccat aaaatgtatc 300
acgtgcatag taaatcttta tatttgctat ggcgttgcac tagaggactt ggactgcaac 360
aagtggatgc gcggaaaatg aaatcttctt caatagccca g 401

<210> 365
<211> 356
<212> DNA
<213> Homo sapien

<400> 365
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taccagagca tcaagtctct gcagcaggtc attcttgggt aaagaaatga cttccacaaa 180
ctctccatcc cctggctttg gcttcggcct tgcgttttcg gcatcatctc cgttaatggt 240
gactgtcacg atgtgtatag tacagtttga caagcctggg tccatacaga ccgctggaga 300
acattcggca atgtcccctt tgtagccagt ttcttcttcg agctcccgga gagcag 356

<210> 366
<211> 1851
<212> DNA
<213> Homo sapien

<400> 366
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cttccgtgtt cttcattctt cttcaatagc cataaatctt ctagctctgg ctggctgttt 120

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cagcaagtat gagagcagtt cttccatatc tatccagcgc atttaaattc gctttttttct     420
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ggccatgctt gttttttgat tcgatatcag caccgtataa gagcagtgct ttggccatta     540
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gcacgagttt tactacttct gaattcccat tggcagaggc cagatgtaga gcagtcctct     780
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cgctcccctg cagcagggga agcagtggca gcaccacttg cacctcttgc tcccaagcgt    1020
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tcacataaac agaattaaaa gcaaagtcac ataagcatct caacagacac agaaaaggca    1680
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<210> 367
<211> 668
<212> DNA
<213> Homo sapien

<400> 367

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accrtataag agcagtgctt tggccattaa tttatctttc attrtagaca gcrtagtgya     180
gagtggtatt tccatactca tctggaatat ttggatcagt gccatgttcc agcaacatta     240
acgcacattc atcttcctgg cattgtacgg cctgtcagta ttagacccaa aaacaaatta     300
catatcttag gaattcaaaa taacattcca cagctttcac caactagtta tatttaaagg     360
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ctactgcata cctttatcag agctgtcctc tttttgttgt caaggacatt aagttgacat     480
cgtctgtcca gcaggagttt tactacttct gaattcccat tggcagaggc cagatgtaga     540
gcagtcctat gagagtgaga agacttttta ggaaattgta gtgcactagc tacagccata     600
gcaatgattc atgtaactgc aaacactgaa tagcctgcta ttactctgcc ttcaaaaaaa     660
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<210> 368
<211> 1512
<212> DNA
<213> Homo sapien

<400> 368

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ttcaaacaga ttggaaaccc ggagttacct gctagttggt gaaactggtt ggtagacgcg     180
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atctgttggc tactactggc ttctcctggc tgttaaaagc agatggtggt tgaggttgat 240
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gaacatggca ctgatccaaa tattccagat gagtatggaa ataccactct rcactaygct 960
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taacattgac gtgtgtaagg gccagtcttc cgtatttgga agctcaagca taacttgaat 1140
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<210> 369
<211> 1853
<212> DNA
<213> Homo sapien

<400> 369
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ggagaatggc atgaacccgg gaggtggagg ttgcagtgag ccgagatccg ccactacact    1800
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<210> 370
<211> 2184
<212> DNA
<213> Homo sapien

<400> 370

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tgtgtctgtt gagatgctta tgtgactttg cttttaattc tgtttatgtg attatcacat     240
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ctcaaaaaaa aaaaaaaaaa aaaa                                           2184
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<210> 371
<211> 1855
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
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<223> n = A,T,C or G

<400> 371
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gccgcccccg cataaccgtc agactggcct gtaacggctt gcaggcgcac gccgcacgcg 180
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<210> 372
<211> 1059
<212> DNA
<213> Homo sapien

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<210> 373
<211> 1155
<212> DNA
<213> Homo sapien

<400> 373
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accagaaata aataa 1155

<210> 374
<211> 2000
<212> DNA
<213> Homo sapien

<400> 374
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<210> 375
<211> 2040
<212> DNA
<213> Homo sapien

<400> 375
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<210> 376
<211> 329
<212> PRT
<213> Homo sapien

<400> 376
Met Asp Ile Val Val Ser Gly Ser His Pro Leu Trp Val Asp Ser Phe

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Glu Tyr Thr Ile Val His Ala Ser Phe Ile Ser Cys Ile Ser Ser Ser
        35                  40                  45
Leu Asp Gly Gln Gly Glu Arg Gln Glu Gln Arg Gly His Phe Trp Arg
    50                  55                  60
Pro Gln Arg Leu Leu Cys Glu Asp Ala Trp Glu Gln Glu Val Gln Val
65                  70                  75                  80
Val Leu Pro Leu Leu Pro Leu Leu Gln Gly Ser Gly Lys Ser Asn Val
                85                  90                  95
Val Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe Met Asp Pro Arg Tyr
            100                 105                 110
His Val His Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp
        115                 120                 125
Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp
    130                 135                 140
Val Asn Lys Arg Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser
145                 150                 155                 160
Ala Asn Gly Asn Ser Glu Val Val Lys Leu Val Leu Asp Arg Arg Cys
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Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Thr Lys Ala
            180                 185                 190
Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly
        195                 200                 205
Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr
    210                 215                 220
Ala Val Tyr Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr
225                 230                 235                 240
Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu
                245                 250                 255
Leu Gly Ile His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys
            260                 265                 270
Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu
        275                 280                 285
Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Pro Leu Leu
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Glu Gln Asn Val Asp Val Ser Ser Gln Asp Leu Glu Arg Arg Pro Glu
305                 310                 315                 320
Ser Met Leu Phe Leu Val Ile Ile Met
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<210> 377
<211> 148
<212> PRT
<213> Homo sapien

<220>
<221> VARIANT
<222> (1)...(148)
<223> Xaa = Any Amino Acid

<400> 377

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Met Thr Xaa Pro Ser Trp Ser Pro Gly Thr Thr Ser Val Glu Lys Ile
 1               5                   10                  15
Trp Thr Ser Ser Thr Glu Leu Pro Trp Trp Gly Lys Val Pro Arg Lys
            20                  25                  30
Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Xaa Asp Lys
```

35 40 45
Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu
50 55 60
Val Val Lys Leu Xaa Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp
65 70 75 80
Asn Lys Lys Arg Thr Ala Leu Xaa Lys Ala Val Gln Cys Gln Glu Asp
85 90 95
Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro
100 105 110
Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Xaa Tyr Asn Glu Asp
115 120 125
Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser
130 135 140
Lys Asn Lys Val
145

<210> 378
<211> 1719
<212> PRT
<213> Homo sapien

<400> 378
Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys
1 5 10 15
Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe
20 25 30
Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp
35 40 45
His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp
50 55 60
Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val
65 70 75 80
Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn
85 90 95
Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser
100 105 110
Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe
115 120 125
Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His
130 135 140
Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met
145 150 155 160
Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala
165 170 175
Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu
180 185 190
Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr
195 200 205
Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met
210 215 220
Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn
225 230 235 240
Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys
245 250 255
Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly
260 265 270
Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val
275 280 285

```
Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr
    290                 295                 300
Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile
305                 310                 315                 320
Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu
                325                 330                 335
Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val
            340                 345                 350
Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile
        355                 360                 365
Ser Ser Glu Asn Ser Asn Pro Glu Asn Val Ser Arg Thr Arg Asn Lys
    370                 375                 380
Pro Arg Thr His Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser
385                 390                 395                 400
Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys
                405                 410                 415
Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly
            420                 425                 430
Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys
        435                 440                 445
Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly
    450                 455                 460
Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys
465                 470                 475                 480
Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys
                485                 490                 495
Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp
            500                 505                 510
Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu
        515                 520                 525
Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp
    530                 535                 540
Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln
545                 550                 555                 560
Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val
                565                 570                 575
Val Lys Leu Leu Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn
            580                 585                 590
Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu
        595                 600                 605
Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp
    610                 615                 620
Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys
625                 630                 635                 640
Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys
                645                 650                 655
Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys
            660                 665                 670
Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala
        675                 680                 685
Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly
    690                 695                 700
Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser
705                 710                 715                 720
Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser
                725                 730                 735
His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln
            740                 745                 750
```

Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys
755 760 765
Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser
770 775 780
Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp
785 790 795 800
Arg Glu Val Glu Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly
805 810 815
Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn
820 825 830
Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe
835 840 845
Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser
850 855 860
Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn
865 870 875 880
Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu
885 890 895
Glu Gly Ser Glu Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile
900 905 910
Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn
915 920 925
Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro
930 935 940
Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu
945 950 955 960
Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe
965 970 975
Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His
980 985 990
Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser
995 1000 1005
Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu
1010 1015 1020
Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His
1025 1030 1035 1040
Gln Ser Gln Leu Pro Arg Thr His Met Val Val Glu Val Asp Ser Met
1045 1050 1055
Pro Ala Ala Ser Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met
1060 1065 1070
Gly Lys Trp Cys Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys
1075 1080 1085
Ser Asn Val Gly Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr
1090 1095 1100
Leu Arg Ser Lys Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys
1105 1110 1115 1120
Arg Gly Ser Gly Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp
1125 1130 1135
Ser Ala Met Lys Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His
1140 1145 1150
Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp
1155 1160 1165
Gly Asp Tyr Asp Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg
1170 1175 1180
Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val
1185 1190 1195 1200
Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys
1205 1210 1215

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Lys Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly
            1220                1225                1230
Asn Ser Glu Val Val Lys Leu Leu Leu Asp Arg Arg Cys Gln Leu Asn
        1235                1240                1245
Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys
    1250                1255                1260
Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro
1265                1270                1275                1280
Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr
                1285                1290                1295
Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp
            1300                1305                1310
Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Val
        1315                1320                1325
His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala
    1330                1335                1340
Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala
1345                1350                1355                1360
Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn
                1365                1370                1375
Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr
            1380                1385                1390
Ala Val Ser Ser His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr
        1395                1400                1405
Lys Glu Lys Gln Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu
    1410                1415                1420
Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly
1425                1430                1435                1440
Ser Glu Asn Ser Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn
                1445                1450                1455
Lys Asp Gly Asp Arg Glu Val Glu Glu Glu Met Lys Lys His Glu Ser
            1460                1465                1470
Asn Asn Val Gly Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly
        1475                1480                1485
Asn Gly Asp Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu
    1490                1495                1500
Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys
1505                1510                1515                1520
Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser
                1525                1530                1535
Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu
            1540                1545                1550
Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Lys Arg Ser
        1555                1560                1565
Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Leu Glu Asn Phe
    1570                1575                1580
Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe
1585                1590                1595                1600
Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly
                1605                1610                1615
Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro
            1620                1625                1630
Asp Thr Glu Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln
        1635                1640                1645
Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile
    1650                1655                1660
Leu Ile His Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser
1665                1670                1675                1680
```

Glu Leu Ser Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn
1685 1690 1695
Ser Thr Leu Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr
1700 1705 1710
Met Lys His Gln Ser Gln Leu
1715

<210> 379
<211> 656
<212> PRT
<213> Homo sapien

<400> 379
Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys
1 5 10 15
Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe
20 25 30
Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp
35 40 45
His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp
50 55 60
Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val
65 70 75 80
Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn
85 90 95
Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser
100 105 110
Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe
115 120 125
Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His
130 135 140
Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met
145 150 155 160
Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala
165 170 175
Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu
180 185 190
Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr
195 200 205
Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met
210 215 220
Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn
225 230 235 240
Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys
245 250 255
Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly
260 265 270
Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val
275 280 285
Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr
290 295 300
Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile
305 310 315 320
Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu
325 330 335
Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val
340 345 350
Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile

```
        355                 360                 365
Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu
    370                 375                 380
Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys
385                 390                 395                 400
Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu
                405                 410                 415
Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn
            420                 425                 430
Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn Gly Leu Ile Pro
        435                 440                 445
Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu
    450                 455                 460
Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu
465                 470                 475                 480
Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp
                485                 490                 495
Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu
            500                 505                 510
Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys
        515                 520                 525
Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly
    530                 535                 540
Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser
545                 550                 555                 560
Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr
                565                 570                 575
His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln
            580                 585                 590
Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln
        595                 600                 605
Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys
    610                 615                 620
Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile
625                 630                 635                 640
Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu
                645                 650                 655

      <210> 380
      <211> 671
      <212> PRT
      <213> Homo sapien

      <400> 380
Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys
1               5                   10                  15
Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe
            20                  25                  30
Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp
        35                  40                  45
His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp
    50                  55                  60
Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val
65                  70                  75                  80
Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn
                85                  90                  95
Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser
            100                 105                 110
```

```
Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe
          115                 120                 125
Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His
    130                 135                 140
Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met
145                 150                 155                 160
Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala
                165                 170                 175
Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu
            180                 185                 190
Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr
        195                 200                 205
Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met
    210                 215                 220
Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn
225                 230                 235                 240
Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys
                245                 250                 255
Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly
            260                 265                 270
Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val
        275                 280                 285
Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr
    290                 295                 300
Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile
305                 310                 315                 320
Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu
                325                 330                 335
Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val
            340                 345                 350
Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile
        355                 360                 365
Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu
    370                 375                 380
Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys
385                 390                 395                 400
Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu
                405                 410                 415
Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn
            420                 425                 430
Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn Gly Leu Ile Pro
        435                 440                 445
Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu
    450                 455                 460
Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu
465                 470                 475                 480
Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp
                485                 490                 495
Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu
            500                 505                 510
Asn Gly Gln Pro Glu Lys Arg Ser Gln Glu Pro Glu Ile Asn Lys Asp
        515                 520                 525
Gly Asp Arg Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys Lys
    530                 535                 540
His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly Ala
545                 550                 555                 560
Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser Arg
                565                 570                 575
```

```
Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr His
            580                 585                 590
Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln Asn
        595                 600                 605
Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln Ile
    610                 615                 620
Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys Lys
625                 630                 635                 640
Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile Ala
                645                 650                 655
Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu
            660                 665                 670
```

<210> 381
<211> 251
<212> DNA
<213> Homo sapien

<400> 381

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ggagaagcgt ctgctggggc aggaaggggt ttccctgccc tctcacctgt ccctcaccaa      60
ggtaacatgc ttcccctaag ggtatcccaa cccaggggcc tcaccatgac ctctgagggg     120
ccaatatccc aggagaagca ttggggagtt gggggcaggt gaaggaccca ggactcacac     180
atcctgggcc tccaaggcag aggagagggt cctcaagaag gtcaggagga aaatccgtaa     240
caagcagtca g                                                          251
```

<210> 382
<211> 3279
<212> DNA
<213> Homo sapiens

<400> 382

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cttcctgcag cccccatgct ggtgaggggc acgggcagga acagtggacc caacatggaa 60
atgctggagg gtgtcaggaa gtgatcgggc tctggggcag ggaggagggg tggggagtgt 120
cactgggagg ggacatcctg cagaaggtag gagtgagcaa acacccgctg caggggaggg 180
gagagccctg cggcacctgg gggagcagag ggagcagcac ctgcccaggc ctgggaggag 240
gggcctggag ggcgtgagga ggagcgaggg ggctgcatgg ctggagtgag ggatcagggg 300
cagggcgcga gatggcctca cacagggaag agagggcccc tcctgcaggg cctcacctgg 360
gccacaggag gacactgctt ttcctctgag gagtcaggag ctgtggatgg tgctggacag 420
aagaaggaca gggcctggct caggtgtcca gaggctgtcg ctggcttccc tttgggatca 480
gactgcaggg agggagggcg gcagggttgt ggggggagtg acgatgagga tgacctgggg 540
gtggctccag gccttgcccc tgcctgggcc ctcacccagc ctccctcaca gtctcctggc 600
cctcagtctc tcccctccac tccatcctcc atctggcctc agtgggtcat tctgatcact 660
gaactgacca tacccagccc tgcccacggc cctccatggc tccccaatgc cctggagagg 720
ggacatctag tcagagagta gtcctgaaga ggtggcctct gcgatgtgcc tgtgggggca 780
gcatcctgca gatggtcccg gccctcatcc tgctgacctg tctgcaggga ctgtcctcct 840
ggaccttgcc ccttgtgcag gagctggacc ctgaagtccc ctccccatag gccaagactg 900
gagccttgtt ccctctgttg gactccctgc ccatattctt gtgggagtgg gttctggaga 960
catttctgtc tgttcctgag agctgggaat tgctctcagt catctgcctg cgcggttctg 1020
agagatggag ttgcctaggc agttattggg gccaatcttt ctcactgtgt ctctcctcct 1080
ttacccttag ggtgattctg gggtccact tgtctgtaat ggtgtgcttc aaggtatcac 1140
atcatggggc cctgagccat gtgccctgcc tgaaaagcct gctgtgtaca ccaaggtggt 1200
gcattaccgg aagtggatca aggacaccat cgcagccaac ccctgagtgc ccctgtccca 1260
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gacctgtgct ttctggtgtg gagtccaggg ctgctaggaa aaggaatggg cagacacagg 1440
tgtatgccaa tgtttctgaa atgggtataa tttcgtcctc tccttcggaa cactggctgt 1500
ctctgaagac ttctcgctca gtttcagtga ggacacacac aaagacgtgg gtgaccatgt 1560
tgtttgtggg gtgcagagat gggaggggtg gggcccaccc tggaagagtg gacagtgaca 1620
```

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caaggtggac actctctaca gatcactgag gataagctgg agccacaatg catgaggcac 1680
acacacagca aggttgacgc tgtaaacata gcccacgctg tcctgggggc actgggaagc 1740
ctagataagg ccgtgagcag aaagaagggg aggatcctcc tatgttgttg aaggagggac 1800
taggggggaga aactgaaagc tgattaatta caggaggttt gttcaggtcc cccaaaccac 1860
cgtcagattt gatgatttcc tagcaggact tacagaaata aagagctatc atgctgtggt 1920
ttattatggt ttgttacatt gataggatac atactgaaat cagcaaacaa aacagatgta 1980
tagattagag tgtggagaaa acagaggaaa acttgcagtt acgaagactg gcaacttggc 2040
tttactaagt tttcagactg gcaggaagtc aaacctatta ggctgaggac cttgtggagt 2100
gtagctgatc cagctgatag aggaactagc caggtgggg cctttccctt tggatggggg 2160
gcatatccga cagttattct ctccaagtgg agacttacgg acagcatata attctccctg 2220
caaggatgta tgataatatg tacaaagtaa ttccaactga ggaagctcac ctgatcctta 2280
gtgtccaggg tttttactgg gggtctgtag gacgagtatg gagtacttga ataattgacc 2340
tgaagtcctc agacctgagg ttccctagag ttcaaacaga tacagcatgg tccagagtcc 2400
cagatgtaca aaaacaggga ttcatcacaa atcccatctt tagcatgaag ggtctggcat 2460
ggcccaaggc cccaagtata tcaaggcact tgggcagaac atgccaagga atcaaatgtc 2520
atctcccagg agttattcaa gggtgagccc tttacttggg atgtacaggc tttgagcagt 2580
gcagggctgc tgagtcaacc ttttattgta caggggatga gggaaaggga gaggatgagg 2640
aagcccccct ggggatttgg tttggtcttg tgatcaggtg gtctatgggg ctatccctac 2700
aaagaagaat ccagaaatag gggcacattg aggaatgata ctgagcccaa agagcattca 2760
atcattgttt tatttgcctt cttttcacac cattggtgag ggagggatta ccaccctggg 2820
gttatgaaga tggttgaaca ccccacacat agcaccggag atatgagatc aacagtttct 2880
tagccataga gattcacagc ccagagcagg aggacgctgc acaccatgca ggatgacatg 2940
ggggatgcgc tcgggattgg tgtgaagaag caaggactgt tagaggcagg ctttatagta 3000
acaagacggt ggggcaaact ctgatttccg tgggggaatg tcatggtctt gctttactaa 3060
gttttgagac tggcaggtag tgaaactcat taggctgaga accttgtgga atgcagctga 3120
cccagctgat agaggaagta gccaggtggg agcctttccc agtgggtgtg ggacatatct 3180
ggcaagattt tgtggcactc ctggttacag atactggggc agcaaataaa actgaatctt 3240
gttttcagac cttaaaaaaa aaaaaaaaaa aaaagtttt                       3279

<210> 383
<211> 154
<212> PRT
<213> Homo sapiens

<400> 383
Met Ala Gly Val Arg Asp Gln Gly Gln Gly Ala Arg Trp Pro His Thr
                5                   10                  15

Gly Lys Arg Gly Pro Leu Leu Gln Gly Leu Thr Trp Ala Thr Gly Gly
            20                  25                  30

His Cys Phe Ser Ser Glu Glu Ser Gly Ala Val Asp Gly Ala Gly Gln
        35                  40                  45

Lys Lys Asp Arg Ala Trp Leu Arg Cys Pro Glu Ala Val Ala Gly Phe
    50                  55                  60

Pro Leu Gly Ser Asp Cys Arg Glu Gly Gly Arg Gln Gly Cys Gly Gly
65                  70                  75                  80

Ser Asp Asp Glu Asp Asp Leu Gly Val Ala Pro Gly Leu Ala Pro Ala
                85                  90                  95

Trp Ala Leu Thr Gln Pro Pro Ser Gln Ser Pro Gly Pro Gln Ser Leu
            100                 105                 110

Pro Ser Thr Pro Ser Ser Ile Trp Pro Gln Trp Val Ile Leu Ile Thr
        115                 120                 125
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Glu Leu Thr Ile Pro Ser Pro Ala His Gly Pro Pro Trp Leu Pro Asn
130 135 140

Ala Leu Glu Arg Gly His Leu Val Arg Glu
145 150

<210> 384
<211> 557
<212> DNA
<213> Homo sapiens

<400> 384
ggatcctcta gagcggccgc ctactactac taaattcgcg gccgcgtcga cgaagaagag 60
aaagatgtgt tttgttttgg actctctgtg gtcccttcca atgctgtggg tttccaacca 120
ggggaagggt ccctttgca ttgccaagtg ccataaccat gagcactact ctaccatggt 180
tctgcctcct ggccaagcag gctggtttgc aagaatgaaa tgaatgattc tacagctagg 240
acttaacctt gaaatggaaa gtcttgcaat cccatttgca ggatccgtct gtgcacatgc 300
ctctgtagag agcagcattc ccagggacct tggaaacagt tggcactgta aggtgcttgc 360
tccccaagac acatcctaaa aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc 420
ccttcttatt tatgtgaaca actgtttgtc tttttttgta tcttttttaa actgtaaagt 480
tcaattgtga aaatgaatat catgcaaata aattatgcga tttttttttc aaagtaaaaa 540
aaaaaaaaaa aaaaaaa 557

<210> 385
<211> 337
<212> DNA
<213> Homo sapiens

<400> 385
ttcccaggtg atgtgcgagg gaagacacat ttactatcct tgatggggct gattccttta 60
gtttctctag cagcagatgg gttaggagga agtgacccaa gtggttgact cctatgtgca 120
tctcaaagcc atctgctgtc ttcgagtacg gacacatcat cactcctgca ttgttgatca 180
aaacgtggag gtgcttttcc tcagctaaga agcccttagc aaaagctcga atagacttag 240
tatcagacag gtccagtttc cgcaccaaca cctgctggtt ccctgtcgtg gtctggatct 300
ctttggccac caattccccc ttttccacat cccggca 337

<210> 386
<211> 300
<212> DNA
<213> Homo sapiens

<400> 386
gggcccgcta ccggcccagg ccccgcctcg cgagtcctcc tccccgggtg cctgcccgca 60
gcccgctcgg cccagagggt gggcgcgggg ctgcctctac cggctggcgg ctgtaactca 120
gcgaccttgg cccgaaggct ctagcaagga cccaccgacc ccagccgcgg cggcggcggc 180
gcggactttg cccggtgtgt ggggcggagc ggactgcgtg tccgcggacg ggcagcgaag 240
atgttagcct tcgctgccag gaccgtggac cgatcccagg gctgtggtgt aacctcagcc 300

<210> 387
<211> 537
<212> DNA
<213> Homo sapiens

<400> 387
gggccgagtc gggcaccaag ggactctttg caggcttcct tcctcggatc atcaaggctg 60
ccccctcctg tgccatcatg atcagcacct atgagttcgg caaaagcttc ttccagaggc 120

tgaaccagga ccggcttctg ggcggctgaa aggggcaagg aggcaaggac cccgtctctc 180
ccacggatgg ggagagggca ggaggagacc cagccaagtg ccttttcctc agcactgagg 240
gagggggctt gtttcccttc cctcccggcg acaagctcca gggcagggct gtccctctgg 300
gcggcccagc acttcctcag acacaacttc ttcctgctgc tccagtcgtg gggatcatca 360
cttacccacc ccccaagttc aagaccaaat cttccagctg ccccсttcgt gtttccctgt 420
gtttgctgta gctgggcatg tctccaggaa ccaagaagcc ctcagcctgg tgtagtctcc 480
ctgacccttg ttaattcctt aagtctaaag atgatgaact tcaaaaaaaa aaaaaaa 537

<210> 388
<211> 520
<212> DNA
<213> Homo sapiens

<400> 388
aggataattt ttaaaccaat caaatgaaaa aaacaaacaa acaaaaaagg aaatgtcatg 60
tgaggttaaa ccagtttgca ttcccctaat gtggaaaaag taagaggact actcagcact 120
gtttgaagat tgcctcttct acagcttctg agaattgtgt tatttcactt gccaagtgaa 180
ggaccccctc cccaacatgc cccagcccac ccctaagcat ggtcccttgt caccaggcaa 240
ccaggaaact gctacttgtg gacctcacca gagaccagga gggtttggtt agctcacagg 300
acttccccca ccccagaaga ttagcatccc atactagact catactcaac tcaactaggc 360
tcatactcaa ttgatggtta ttagacaatt ccatttcttt ctggttatta taaacagaaa 420
atctttcctc ttctcattac cagtaaaggc tcttggtatc tttctgttgg aatgatttct 480
atgaacttgt cttattttaa tggtgggttt tttttctggt 520

<210> 389
<211> 365
<212> DNA
<213> Homo sapiens

<400> 389
cgttgccсca gtttgacaga aggaaaggcg gagcttattc aaagtctaga gggagtggag 60
gagttaaggc tggatttcag atctgcctgg ttccagccgc agtgtgccct ctgctccccc 120
aacgactttc caaataatct caccagcgcc ttccagctca ggcgtcctag aagcgtcttg 180
aagcctatgg ccagctgtct ttgtgttccc tctcacccgc ctgtcctcac agctgagact 240
cccaggaaac cttcagacta ccttcctctg ccttcagcaa ggggcgttgc ccacattctc 300
tgagggtcag tggaagaacc tagactccca ttgctagagg tagaaagggg aagggtgctg 360
gggag 365

<210> 390
<211> 221
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(221)
<223> n = A,T,C or G

<400> 390
tgcctctcca tcctggcccc gacttctctg tcaggaaagt ggggatggac cccatctgca 60
tacacggntt ctcatgggtg tggaacatct ctgcttgcgg tttcaggaag gcctctggct 120
gctctangag tctgancnga ntcgttgccc cantntgaca naaggaaagg cggagcttat 180
tcaaagtcta gagggagtgg aggagttaag gctggatttc a 221

<210> 391
<211> 325
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(325)
<223> n = A,T,C or G

<400> 391
tggagcaggt cccgaggcct ccctagagcc tggggccgac tctgtgncga tgcangcttt 60
ctctcgcgcc cagcctggag ctgctcctgg catctaccaa caatcagncg aggcgagcag 120
tagccagggc actgctgcca acagccagtc cnnataccat catgtnaccc ggtgngctct 180
naanttngat ntccanagcc ctacccatcn tagttctgct ctcccaccgg ntaccagccc 240
cactgcccag gaatcctaca gccagtaccc tgtcccgacg tctctaccta ccagtacgat 300
gagacctccg gctactacta tgacc 325

<210> 392
<211> 277
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(277)
<223> n = A,T,C or G

<400> 392
atattgttta actccttcct ttatatcttt taacattttc atggngaaag gttcacatct 60
agtctcactt nggcnagngn ctcctacttg agtctcttcc ccggcctgnn ccagtngnaa 120
antaccanga accgncatgn cttaanaacn ncctggtttn tgggttnntc aatgactgca 180
tgcagtgcac caccctgtcc actacgtgat gctgtaggat taaagtctca cagtgggcgg 240
ctgaggatac agcgccgcgt cctgtgttgc tggggaa 277

<210> 393
<211> 566
<212> DNA
<213> Homo sapiens

<400> 393
actagtccag tgtggtggaa ttcgcggccg cgtcgacgga caggtcagct gtctggctca 60
gtgatctaca ttctgaagtt gtctgaaaat gtcttcatga ttaaattcag cctaaacgtt 120
ttgccgggaa cactgcagag acaatgctgt gagtttccaa ccttagccca tctgcgggca 180
gagaaggtct agtttgtcca tcagcattat catgatatca ggactggtta cttggttaag 240
gaggggtcta ggagatctgt ccctttttaga gacaccttac ttataatgaa gtatttggga 300
gggtggtttt caaaagtaga aatgtcctgt attccgatga tcatcctgta aacattttat 360
catttattaa tcatccctgc ctgtgtctat tattatattc atatctctac gctggaaact 420
ttctgcctca atgtttactg tgcctttgtt tttgctagtt tgtgttgttg aaaaaaaaaa 480
cattctctgc ctgagtttta atttttgtcc aaagttattt taatctatac aattaaaagc 540
ttttgcctat caaaaaaaaa aaaaaa 566

<210> 394
<211> 384
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(384)
<223> n = A,T,C or G

<400> 394
gaacatacat gtcccggcac ctgagctgca gtctgacatc atcgccatca cgggcctcgc 60
tgcaaattng gaccgggcca aggctggact gctggagcgt gtgaaggagc tacaggccna 120
gcaggaggac cggctttaa ggagttttaa gctgagtgtc actgtagacc ccaaatacca 180
tcccaagatt atcgggagaa agggggcagt aattacccaa atccggttgg agcatgacgt 240
gaacatccag tttcctgata aggacgatgg gaaccagccc caggaccaaa ttaccatcac 300
agggtacgaa aagaacacag aagctgccag ggatgctata ctgagaattg tgggtgaact 360
tgagcagatg gtttctgagg acgt 384

<210> 395
<211> 399
<212> DNA
<213> Homo sapiens

<400> 395
ggcaaaactg tgtgacctca ataagacctc gcagatccaa ggtcaagtat cagaagtgac 60
tctgaccttg gactccaaga cctacatcaa cagcctggct atattagatg atgagccagt 120
tatcagaggt ttcatcattg cggaaattgt ggagtctaag gaaatcatgg cctctgaagt 180
attcacgtct ttccagtacc ctgagttctc tatagagttg cctaacacag gcagaattgg 240
ccagctactt gtctgcaatt gtatcttcaa gaataccctg gccatccctt tgactgacgt 300
caagttctct ttggaaagcc tgggcatctc ctcactacag acctctgacc atgggacggt 360
gcagcctggt gagaccatcc aatcccaaat aaaatgcac 399

<210> 396
<211> 403
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(403)
<223> n = A,T,C or G

<400> 396
tggagttntc agtgcaaaca agccataaag cttcagtagc aaattactgt ctcacagaaa 60
gacattttca acttctgctc cagctgctga taaaacaaat catgtgttta gcttgactcc 120
agacaaggac aacctgttcc ttcataactc tctagagaaa aaaaggagtt gttagtagat 180
actaaaaaaa gtggatgaat aatctggata tttttcctaa aaagattcct tgaaacacat 240
taggaaaatg gagggcctta tgatcagaat gctagaatta gtccattgtg ctgaagcagg 300
gtttagggga gggagtgagg gataaaagaa ggaaaaaaag aagagtgaga aaacctattt 360
atcaaagcag gtgctatcac tcaatgttag gccctgctct ttt 403

<210> 397
<211> 100
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(100)
<223> n = A,T,C or G

<400> 397
actagtncag tgtggtggaa ttcgcggccg cgtcgaccta naanccatct ctatagcaaa 60
tccatccccg ctcctggttg gtnacagaat gactgacaaa 100

<210> 398
<211> 278

<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(278)
<223> n = A,T,C or G

<400> 398
gcggccgcgt cgacagcagt tccgccagcg ctcgcccctg ggtggggatg tgctgcacgc 60
ccacctggac atctggaagt cagcggcctg gatgaaagag cggacttcac ctggggcgat 120
tcactactgt gcctcgacca gtgaggagag ctggaccgac agcgaggtgg actcatcatg 180
ctccgggcag cccatccacc tgtggcagtt cctcaaggag ttgctactca agccccacag 240
ctatggccgc ttcattangt ggctcaacaa ggagaagg 278

<210> 399
<211> 298
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(298)
<223> n = A,T,C or G

<400> 399
acggaggtgg aggaagcgnc cctgggatcg anaggatggg tcctgncatt gaccncctcn 60
ggggtgccng catggagcgc atgggcgcgg gcctgggcca cggcatggat cgcgtgggct 120
ccgagatcga gcgcatgggc ctggtcatgg accgcatggg ctccgtggag cgcatgggct 180
ccggcattga gcgcatgggc ccgctgggcc tcgaccacat ggcctccanc attgancgca 240
tgggccagac catggagcgc attggctctg gcgtggagcn catgggtgcc ggcatggg 298

<210> 400
<211> 548
<212> DNA
<213> Homo sapiens

<400> 400
acatcaacta cttcctcatt ttaaggtatg gcagttccct tcatcccctt ttcctgcctt 60
gtacatgtac atgtatgaaa tttccttctc ttaccgaact ctctccacac atcacaaggt 120
caaagaacca cacgcttaga agggtaagag ggcaccctat gaaatgaaat ggtgatttct 180
tgagtctctt ttttccacgt ttaaggggcc atggcaggac ttagagttgc gagttaagac 240
tgcagagggc tagagaatta tttcatacag gctttgaggc cacccatgtc acttatcccg 300
tataccctct caccatcccc ttgtctactc tgatgccccc aagatgcaac tgggcagcta 360
gttggcccca taattctggg cctttgttgt ttgttttaat tacttgggca tcccaggaag 420
ctttccagtg atctcctacc atgggccccc ctcctgggat caagcccctc ccaggccctg 480
tccccagccc ctcctgcccc agcccacccg cttgccttgg tgctcagccc tcccattggg 540
agcaggtt 548

<210> 401
<211> 355
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(355)
<223> n = A,T,C or G

<400> 401
actgtttcca tgttatgttt ctacacattg ctacctcagt gctcctggaa acttagcttt 60
tgatgtctcc aagtagtcca ccttcattta actctttgaa actgtatcat ctttgccaag 120
taagagtggt ggcctatttc agctgctttg acaaaatgac tggctcctga cttaacgttc 180
tataaatgaa tgtgctgaag caaagtgccc atggtggcgg cgaagaagan aaagatgtgt 240
tttgttttgg actctctgtg gtcccttcca atgctgnggg tttccaacca ggggaagggt 300
ccctttgca ttgccaagtg ccataaccat gagcactact ctaccatggn tctgc 355

<210> 402
<211> 407
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(407)
<223> n = A,T,C or G

<400> 402
atggggcaag ctggataaag aaccaagacc cactggagta tgctgtcttc aagaaaccca 60
tctcacatgc ggtggcatac ataggctcaa aataaaggaa tggagaaaaa tatttcaagc 120
aaatggaaaa cagaaaaaag caggtgttgc actcctactt tctgacaaaa cagactatgc 180
gaataaagat aaaaaagaga aggacattac aaaggtggtc ctgacctttg ataaatctca 240
ttgcttgata ccaacctggg ctgttttaat tgcccaaacc aaaaggataa tttgctgagg 300
ttgtggagct tctcccctgc agagagtccc tgatctccca aaatttggtt gagatgtaag 360
gntgattttg ctgacaactc cttttctgaa gttttactca tttccaa 407

<210> 403
<211> 303
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(303)
<223> n = A,T,C or G

<400> 403
cagtatttat agccnaactg aaaagctagt agcaggcaag tctcaaatcc aggcaccaaa 60
tcctaagcaa gagccatggc atggtgaaaa tgcaaaagga gagtctggcc aatctacaaa 120
tagagaacaa gacctactca gtcatgaaca aaaggcaga caccaacatg gatctcatgg 180
gggattggat attgtaatta tagagcagga agatgacagt gatcgtcatt tggcacaaca 240
tcttaacaac gaccgaaacc cattatttac ataaacctcc attcggtaac catgttgaaa 300
gga 303

<210> 404
<211> 225
<212> DNA
<213> Homo sapiens

<400> 404
aagtgtaact tttaaaaatt tagtggattt tgaaaattct tagaggaaag taaaggaaaa 60
attgttaatg cactcattta cctttacatg gtgaaagttc tctcttgatc ctacaaacag 120
acattttcca ctcgtgtttc catagttgtt aagtgtatca gatgtgttgg gcatgtgaat 180
ctccaagtgc ctgtgtaata aataaagtat ctttatttca ttcat 225

<210> 405

<211> 334
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(334)
<223> n = A,T,C or G

<400> 405
gagctgttat actgtgagtt ctactaggaa atcatcaaat ctgagggttg tctggaggac 60
ttcaatacac ctccccccat agtgaatcag cttccagggg gtccagtccc tctccttact 120
tcatccccat cccatgccaa aggaagaccc tccctccttg gctcacagcc ttctctaggc 180
ttcccagtgc ctccaggaca gagtgggtta tgttttcagc tccatccttg ctgtgagtgt 240
ctggtgcggt tgtgcctcca gcttctgctc agtgcttcat ggacagtgtc cagcccatgt 300
cactctccac tctctcanng tggatcccac ccct 334

<210> 406
<211> 216
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(216)
<223> n = A,T,C or G

<400> 406
tttcatacct aatgagggag ttganatnac atnnaaccag gaaatgcatg gatctcaang 60
gaaacaaaca cccaataaac tcggagtggc agactgacaa ctgtgagaca tgcacttgct 120
acnaaacaca aatttnatgt tgcacccttg tttctacacc tgtgggttat gacaaagaca 180
actgccaaag aatnttcaag aaggaggact gccant 216

<210> 407
<211> 413
<212> DNA
<213> Homo sapiens

<400> 407
gctgacttgc tagtatcatc tgcattcatt gaagcacaag aacttcatgc cttgactcat 60
gtaaatgcaa taggattaaa aaataaattt gatatcacat ggaaacagac aaaaaatatt 120
gtacaacatt gcacccagtg tcagattcta cacctggcca ctcaggaagc aagagttaat 180
cccagaggtc tatgtcctaa tgtgttatgg caaatggatg tcatgcacgt accttcattt 240
ggaaaattgt catttgtcca tgtgacagtt gatacttatt cacatttcat atgggcaacc 300
tgccagacag gagaaagtct tcccatgtta aaagacattt attatcttgt tttcctgtca 360
tgggagttcc agaaaaagtt aaaacagaca atgggccagg ttctgtagta aag 413

<210> 408
<211> 183
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(183)
<223> n = A,T,C or G

<400> 408

ggagctngcc ctcaattcct ccatntctat gttancatat ttaatgtctt ttgnnattaa 60
tncttaacta gttaatcctt aaagggctan ntaatcctta actagtccct ccattgtgag 120
cattatcctt ccagtattcn ccttctnttt tatttactcc ttcctggcta cccatgtact 180
ntt 183

<210> 409
<211> 250
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(250)
<223> n = A,T,C or G

<400> 409
cccacgcatg ataagctctt tatttctgta agtcctgcta ggaaatcatc aaatctgacg 60
gtggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctcccccta 120
gtccctcctt caacaacata ggaggatcct ccccttcttt ctgctcacgg ccttatctag 180
gcttcccagt gcccccagga cagcgtgggc tatgtttaca gcgcntcctt gctggggggg 240
ggccntatgc 250

<210> 410
<211> 306
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(306)
<223> n = A,T,C or G

<400> 410
ggctggtttg caagaatgaa atgaatgatt ctacagctag gacttaacct tgaaatggaa 60
agtcttgcaa tcccatttgc aggatccgtc tgtgcacatg cctctgtaga gagcagcatt 120
cccagggacc ttggaaacag ttggcactgt aaggtgcttg ctccccaaga cacatcctaa 180
aaggtgttgt aatggtgaaa accgcttcct tctttattgc cccttcttat ttatgtgaac 240
nactggttgg ctttttttgn atcttttta aactggaaag ttcaattgng aaaatgaata 300
tcntgc 306

<210> 411
<211> 261
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(261)
<223> n = A,T,C or G

<400> 411
agagatattn cttaggtnaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa ggngaggcaa a 261

<210> 412

<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 412
gttcaatgtt acctgacatt tctacaacac cccactcacc gatgtattcg ttgcccagtg 60
ggaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgcccagg aaatactacg 120
actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggaggggag 180
ctgggagatt tcactgggta cattgaattc ccaaactacc cangcaatta cccagccaac 240
a 241

<210> 413
<211> 231
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(231)
<223> n = A,T,C or G

<400> 413
aactcttaca atccaagtga ctcatctgtg tgcttgaatc ctttccactg tctcatctcc 60
ctcatccaag tttctagtac cttctctttg ttgtgaagga taatcaaact gaacaacaaa 120
aagtttactc tcctcatttg gaacctaaaa actctcttct tcctgggtct gagggctcca 180
agaatccttg aatcanttct cagatcattg gggacaccan atcaggaacc t 231

<210> 414
<211> 234
<212> DNA
<213> Homo sapiens

<400> 414
actgtccatg aagcactgag cagaagctgg aggcacaacg caccagacac tcacagcaag 60
gatggagctg aaaacataac ccactctgtc ctggaggcac tgggaagcct agagaaggct 120
gtgagccaag gagggagggt cttcctttgg catgggatgg ggatgaagta aggagaggga 180
ctggaccccc tggaagctga ttcactatgg ggggaggtgt attgaagtcc tcca 234

<210> 415
<211> 217
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(217)
<223> n = A,T,C or G

<400> 415
gcataggatt aagactgagt atcttttcta cattctttta actttctaag gggcacttct 60
caaaacacag accaggtagc aaatctccac tgctctaagg ntctcaccac cactttctca 120
cacctagcaa tagtagaatt cagtcctact tctgaggcca gaagaatggt tcagaaaaat 180
antggattat aaaaaataac aattaagaaa aataatc 217

<210> 416
<211> 213
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(213)
<223> n = A,T,C or G

<400> 416
atgcatatnt aaagganact gcctcgcttt tagaagacat ctggnctgct ctctgcatga 60
ggcacagcag taaagctctt tgattcccag aatcaagaac tctcccttc agactattac 120
cgaatgcaag gtggttaatt gaaggccact aattgatgct caaatagaag gatattgact 180
atattggaac agatggagtc tctactacaa aag 213

<210> 417
<211> 303
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(303)
<223> n = A,T,C or G

<400> 417
nagtcttcag gcccatcagg gaagttcaca ctggagagaa gtcatacata tgtactgtat 60
gtgggaaagg ctttactctg agttcaaatc ttcaagccca tcagagagtc cacactggag 120
agaagccata caaatgcaat gagtgtggga agagcttcag gagggattcc cattatcaag 180
ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaagggct 240
tcantcaaag ttcgtatctt caaatccatc ngaaggncca cagtatanan aaacctttta 300
agt 303

<210> 418
<211> 328
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(328)
<223> n = A,T,C or G

<400> 418
tttttggcgg tggtggggca gggacgggac angagtctca ctctgttgcc caggctggag 60
tgcacaggca tgatctcggc tcactacaac ccctgcctcc catgtccaag cgattcttgt 120
gcctcagcct tccctgtagc tagaattaca ggcacatgcc accacaccca gctagttttt 180
gtatttttag tagagacagg gtttcaccat gttggccagg ctggtctcaa actcctnacc 240
tcagnggtca ggctggtctc aaactcctga cctcaagtga tctgcccacc tcagcctccc 300
aaagtgctan gattacaggc cgtgagcc 328

<210> 419
<211> 389
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(389)
<223> n = A,T,C or G

<400> 419
cctcctcaag acggcctgtg gtccgcctcc cggcaaccaa gaagcctgca gtgccatatg 60
acccctgagc catggactgg agcctgaaag gcagcgtaca ccctgctcct gatcttgctg 120
cttgtttcct ctctgtggct ccattcatag cacagttgtt gcactgaggc ttgtgcaggc 180
cgagcaaggc caagctggct caaagagcaa ccagtcaact ctgccacggt gtgccaggca 240
ccggttctcc agccaccaac ctcactcgct cccgcaaatg gcacatcagt tcttctaccc 300
taaaggtagg accaaagggc atctgctttt ctgaagtcct ctgctctatc agccatcacg 360
tggcagccac tcnggctgtg tcgacgcgg 389

<210> 420
<211> 408
<212> DNA
<213> Homo sapiens

<400> 420
gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtcctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg aagtgctatg acaaacctgg caagcccg 408

<210> 421
<211> 352
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(352)
<223> n = A,T,C or G

<400> 421
gctcaaaaat ctttttactg atnggcatgg ctacacaatc attgactatt acggaggcca 60
gaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120
ttcactgaca gaacaggtct tttttgggtc cttcttctcc accacnatat acttgcagtc 180
ctccttcttg aagattcttt ggcagttgtc tttgtcataa cccacaggtg tagaaacaag 240
ggtgcaacat gaaatttctg tttcgtagca agtgcatgtc tcacaagttg gcangtctgc 300
cactccgagt ttattgggtg tttgtttcct ttgagatcca tgcatttcct gg 352

<210> 422
<211> 337
<212> DNA
<213> Homo sapiens

<400> 422
atgccaccat gctggcaatg cagcgggcgg tcgaaggcct gcatatccag cccaagctgg 60
cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaagcg gtggtcaagg 120
gcgatagcaa ggtgccggcg atcgcggcgg cgtcaatcct ggccaaggtc agccgtgatc 180
gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcggcggg cataagggct 240
atccgacacc ggtgcacctg gaagccttgc agcggctggg gccgacgccg attcaccgac 300
gcttcttccg ccggtacggc tggcctatga aaattat 337

<210> 423
<211> 310
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(310)
<223> n = A,T,C or G

<400> 423
gctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60
aggagaatga ggcctggcct gggagccctg tgcctactan aagcncatta gattatccat 120
tcactgacag aacaggtctt ttttgggtcc ttcttctcca ccacgatata cttgcagtcc 180
tccttcttga agattctttg gcagttgtct ttgtcataac ccacaggtgt anaaacaagg 240
gtgcaacatg aaatttctgt ttcgtagcaa gtgcatgtct cacagttgtc aagtctgccc 300
tccgagttta 310

<210> 424
<211> 370
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(370)
<223> n = A,T,C or G

<400> 424
gctcaaaaat ctttttactg ataggcatgg ctacacaatc attgactatt agaggccaga 60
ggagaatgag gcctggcctg ggagccctgt gcctactaga agcacattag attatccatt 120
cactgacaga acaggtcttt tttgggtcct tcttctccac cacgatatac ttgcagtcct 180
ccttcttgaa gattctttgg cagttgtctt tgtcataacc cacaggtgta gaaacatcct 240
ggttgaatct cctggaactc cctcattagg tatgaaatag catgatgcat tgcataaagt 300
cacgaaggtg gcaaagatca caacgctgcc cagganaaca ttcattgtga taagcaggac 360
tccgtcgacg 370

<210> 425
<211> 216
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(216)
<223> n = A,T,C or G

<400> 425
aattgctatn ntttattttg ccactcaaaa taattaccaa aaaaaaaaaa tnttaaatga 60
taacaacnca acatcaaggn aaananaaca ggaatggntg actntgcata aatnggccga 120
anattatcca ttatnttaag ggttgacttc aggntacagc acacagacaa acatgcccag 180
gaggntntca ggaccgctcg atgtnttntg aggagg 216

<210> 426
<211> 596
<212> DNA
<213> Homo sapiens

<400> 426
cttccagtga ggataaccct gttgccccgg gccgaggttc tccattaggc tctgattgat 60
tggcagtcag tgatggaagg gtgttctgat cattccgact gccccaaggg tcgctggcca 120
gctctctgtt ttgctgagtt ggcagtagga cctaatttgt taattaagag tagatggtga 180
gctgtccttg tattttgatt aacctaatgg ccttcccagc acgactcgga ttcagctgga 240
gacatcacgg caacttttaa tgaaatgatt tgaagggcca ttaagaggca cttcccgtta 300
ttaggcagtt catctgcact gataacttct tggcagctga gctggtcgga gctgtggccc 360
aaacgcacac ttggcttttg gttttgagat acaactctta atcttttagt catgcttgag 420
ggtggatggc cttttcagct ttaacccaat ttgcactgcc ttggaagtgt agccaggaga 480
atacactcat atactcgtgg gcttagaggc cacagcagat gtcattggtc tactgcctga 540
gtcccgctgg tcccatccca ggaccttcca tcggcgagta cctgggagcc cgtgct 596

<210> 427
<211> 107
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(107)
<223> n = A,T,C or G

<400> 427
gaagaattca agttaggttt attcaaaggg cttacngaga atcctanacc caggncccag 60
cccgggagca gccttanaga gctcctgttt gactgcccgg ctcagng 107

<210> 428
<211> 38
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(38)
<223> n = A,T,C or G

<400> 428
gaacttccna anaangactt tattcactat tttacatt 38

<210> 429
<211> 544
<212> DNA
<213>. Homo sapiens

<400> 429
ctttgctgga cggaataaaa gtggacgcaa gcatgacctc ctgatgaggg cgctgcattt 60
attgaagagc ggctgcagcc ctgcggttca gattaaaatc cgagaattgt atagacgccg 120
atatccacga actcttgaag gactttctga tttatccaca atcaaatcat cggttttcag 180
tttggatggt ggctcatcac ctgtagaacc tgacttggcc gtggctggaa tccactcgtt 240
gccttccact tcagttacac ctcactcacc atcctctcct gttggttctg tgctgcttca 300
agatactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
tgatgtgcag ttaaaaaatc tgcccttttа tgatgtcctt gatgttctca tcaagcccac 420
gagtttagtt caaagcagta ttcagcgatt tcaagagaag ttttttattt ttgctttgac 480
acctcaacaa gttagagaga tatgcatatc cagggatttt ttgccaggtg gtaggagaga 540
ttat 544

<210> 430

<211> 507
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(507)
<223> n = A,T,C or G

<400> 430
cttatcncaa tggggctccc aaacttggct gtgcagtgga aactccgggg gaattttgaa 60
gaacactgac acccatcttc caccccgaca ctctgattta attgggctgc agtgagaaca 120
gagcatcaat ttaaaaagct gcccagaatg ttntcctggg cagcgttgtg atctttgccn 180
ccttcgtgac tttatgcaat gcatcatgct atttcatacc taatgaggga gttccaggag 240
attcaaccag gatgtttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300
caagaaggag gactgcaagt atatcgtggt ggagaagaag gacccaaaaa agacctgttc 360
tgtcagtgaa tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420
cattctcctc tggcctctaa tagtcaatga ttgtgtagcc atgcctatca gtaaaaagat 480
ttttgagcaa aaaaaaaaaa aaaaaaa 507

<210> 431
<211> 392
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(392)
<223> n = A,T,C or G

<400> 431
gaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60
aaacaagaaa gcacttatca ggaggactta caaatggaag tacactctan aaccatcatc 120
tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180
aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtcctgggtt ttccaacaga 240
catcattcca gcattctgag attagggnga ttggggatca ttctggagtt ggaatgttca 300
acaaaagtga tgttgttagg taaaatgtac aacttctgga tctatgcaga cattgaaggt 360
gcaatgagtc tggcttttac tctgctgttt ct 392

<210> 432
<211> 387
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(387)
<223> n = A,T,C or G

<400> 432
ggtatccnta cataatcaaa tatagctgta gtacatgttt tcattggngt agattaccac 60
aaatgcaagg caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg 120
ngtagtccaa gctctcggna gtccagccac tgngaaacat gctcccttta gattaacctc 180
gtggacnctn ttgttgnatt gtctgaactg tagngccctg tattttgctt ctgtctgnga 240
attctgttgc ttctggggca tttccttgng atgcagagga ccaccacaca gatgacagca 300
atctgaattg ntccaatcac agctgcgatt aagacatact gaaatcgtac aggaccggga 360
acaacgtata gaacactgga gtccttt 387

<210> 433
<211> 281
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(281)
<223> n = A,T,C or G

<400> 433
ttcaactagc anagaanact gcttcagggn gtgtaaaatg aaaggcttcc acgcagttat 60
ctgattaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120
caggcnctat ttgggttggc tggaggagct gtggaaaaca tggagagatt ggcgctggag 180
atcgccgtgg ctattcctcn ttgntattac accagngagg ntctctgtnt gcccactggt 240
tnnaaaaccg ntatacaata atgatagaat aggacacaca t 281

<210> 434
<211> 484
<212> DNA
<213> Homo sapiens

<400> 434
ttttaaaata agcatttagt gctcagtccc tactgagtac tctttctctc ccctcctctg 60
aatttaattc tttcaacttg caatttgcaa ggattacaca tttcactgtg atgtatattg 120
tgttgcaaaa aaaaaaaagt gtctttgttt aaaattactt ggtttgtgaa tccatcttgc 180
tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240
agctagtcta tcagcatctg acaggtgaat tggatggttc tcagaaccat ttcacccaga 300
cagcctgttt ctatcctgtt taataaatta gtttgggttc tctacatgca taacaaaccc 360
tgctccaatc tgtcacataa aagtctgtga cttgaagttt agtcagcacc cccaccaaac 420
tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaag tacccatgtc 480
ttta 484

<210> 435
<211> 424
<212> DNA
<213> Homo sapiens

<400> 435
gcgccgctca gagcaggtca ctttctgcct tccacgtcct ccttcaagga agccccatgt 60
gggtagcttt caatatcgca ggttcttact cctctgcctc tataagctca aacccaccaa 120
cgatcgggca agtaaacccc ctccctcgcc gacttcggaa ctggcgagag ttcagcgcag 180
atgggcctgt ggggaggggg caagatagat gagggggagc ggcatggtgc ggggtgaccc 240
cttggagaga ggaaaaaggc cacaagaggg gctgccaccg ccactaacgg agatggccct 300
ggtagagacc tttgggggtc tggaacctct ggactcccca tgctctaact cccacactct 360
gctatcagaa acttaaactt gaggattttc tctgtttttc actcgcaata aattcagagc 420
aaac 424

<210> 436
<211> 667
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(667)
<223> n = A,T,C or G

<400> 436
accttgggaa nactctcaca atataaaggg tcgtagactt tactccaaat tccaaaaagg 60
tcctggccat gtaatcctga aagttttccc aaggtagcta taaaatcctt ataagggtgc 120
agcctcttct ggaattcctc tgatttcaaa gtctcactct caagttcttg aaaacgaggg 180
cagttcctga aaggcaggta tagcaactga tcttcagaaa gaggaactgt gtgcaccggg 240
atgggctgcc agagtaggat aggattccag atgctgacac cttctggggg aaacagggct 300
gccaggtttg tcatagcact catcaaagtc cggtcaacgt ctgtgcttcg aatataaacc 360
tgttcatgtt tataggactc attcaagaat tttctatatc tctttcttat atactctcca 420
agttcataat gctgctccat gcccagctgg gtgagttggc caaatccttg tggccatgag 480
gattccttta tggggtcagt gggaaaggtg tcaatgggac ttcggtctcc atgccgaaac 540
accaaagtca caaacttcaa ctccttggct agtacacttc ggtctagcca gaaaaaaagc 600
agaaacaaga agccaaggct aaggcttgct gccctgccag gaggaggggt gcagctctca 660
tgttgag 667

<210> 437
<211> 693
<212> DNA
<213> Homo sapiens

<400> 437
ctacgtctca accctcattt ttaggtaagg aatcttaagt ccaaagatat taagtgactc 60
acacagccag gtaaggaaag ctggattggc acactaggac tctaccatac cgggttttgt 120
taaagctcag gttaggaggc tgataagctt ggaaggaact tcagacagct tttcagatc 180
ataaaagata attcttagcc catgttcttc tccagagcag acctgaaatg acagcacagc 240
aggtactcct ctattttcac ccctcttgct tctactctct ggcagtcaga cctgtgggag 300
gccatgggag aaagcagctc tctggatgtt tgtacagatc atggactatt ctctgtggac 360
catttctcca ggttacccta ggtgtcacta ttggggggac agccagcatc tttagctttc 420
atttgagttt ctgtctgtct tcagtagagg aaacttttgc tcttcacact tcacatctga 480
acacctaact gctgttgctc ctgaggtggt gaaagacaga tatagagctt acagtattta 540
tcctatttct aggcactgag ggctgtgggg taccttgtgg tgccaaaaca gatcctgttt 600
taaggacatg ttgcttcaga gatgtctgta actatctggg ggctctgttg gctctttacc 660
ctgcatcatg tgctctcttg gctgaaaatg acc 693

<210> 438
<211> 360
<212> DNA
<213> Homo sapiens

<400> 438
ctgcttatca caatgaatgt tctcctgggc agcgttgtga tctttgccac cttcgtgact 60
ttatgcaatg catcatgcta tttcatacct aatgagggag ttccaggaga ttcaaccagg 120
atgtttctac acctgtgggt tatgacaaag acaactgcca aagaatcttc aagaaggagg 180
actgcaagta tatctggtgg agaagaagga cccaaaaaag acctgttctg tcagtgaatg 240
gataatctaa tgtgcttcta gtaggcacag ggctcccagg ccaggcctca ttctcctctg 300
gcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360

<210> 439
<211> 431
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(431)
<223> n = A,T,C or G

<400> 439
gttcctnnta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60

tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtcctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag t 431

<210> 440
<211> 523
<212> DNA
<213> Homo sapiens

<400> 440
agagataaag cttaggtcaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
taaaaattaa aacctctttg tgtcccttgg tcctggaaca tttatgttcc ttttaaagaa 420
acaaaaatca aactttacag aaagatttga tgtatgtaat acatatagca gctcttgaag 480
tatatatatc atagcaaata agtcatctga tgagaacaag cta 523

<210> 441
<211> 430
<212> DNA
<213> Homo sapiens

<400> 441
gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtcctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag 430

<210> 442
<211> 362
<212> DNA
<213> Homo sapiens

<400> 442
ctaaggaatt agtagtgttc ccatcacttg tttggagtgt gctattctaa aagattttga 60
tttcctggaa tgacaattat attttaactt tggtggggga aagagttata ggaccacagt 120
cttcacttct gatacttgta aattaatctt ttattgcact tgttttgacc attaagctat 180
atgtttagaa atggtcattt tacggaaaaa ttagaaaaat tctgataata gtgcagaata 240
aatgaattaa tgttttactt aatttatatt gaactgtcaa tgacaaataa aaattctttt 300
tgattatttt ttgttttcat ttaccagaat aaaaactaag aattaaaagt ttgattacag 360
tc 362

<210> 443
<211> 624
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(624)
<223> n = A,T,C or G

<400> 443
tttttttttt gcaacacaat atacatcaca gtgaaatgtg taatccttgc aaattgcaag 60
ttgaaagaat taaattcaga ggaggggaga gaaagagtac tcagtaggga ctgagcacta 120
aatgcttatt ttaaaagaaa tgtaaagagc agaaagcaat tcaggctacc ctgccttttg 180
tgctggctag tactccggtc ggtgtcagca gcacgtggca ttgaacattg caatgtggag 240
cccaaaccac agaaaatggg gtgaaattgg ccaactttct attaacttgg cttcctgttt 300
tataaaatat tgtgaataat atcacctact tcaaagggca gttatgaggc ttaaatgaac 360
taacgcctac aaaacactta aacatagata acataggtgc aagtactatg tatctggtac 420
atggtaaaca tccttattat taaagtcaac gctaaaatga atgtgtgtgc atatgctaat 480
agtacagaga gagggcactt aaaccaacta agggcctgga gggaaggttt cctggaaaga 540
ngatgcttgt gctgggtcca aatcttggtc tactatgacc ttggccaaat tatttaaact 600
ttgtccctat ctgctaaaca gatc 624

<210> 444
<211> 425
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(425)
<223> n = A,T,C or G

<400> 444
gcacatcatt nntcttgcat tctttgagaa taagaagatc agtaaatagt tcagaagtgg 60
gaagctttgt ccaggcctgt gtgtgaaccc aatgttttgc ttagaaatag aacaagtaag 120
ttcattgcta tagcataaca caaaatttgc ataagtggtg gtcagcaaat ccttgaatgc 180
tgcttaatgt gagaggttgg taaaatcctt tgtgcaacac tctaactccc tgaatgtttt 240
gctgtgctgg gacctgtgca tgccagacaa ggccaagctg gctgaaagag caaccagcca 300
cctctgcaat ctgccacctc ctgctggcag gatttgtttt tgcatcctgt gaagagccaa 360
ggaggcacca gggcataagt gagtagactt atggtcgacg cggccgcgaa tttagtagta 420
gtaga 425

<210> 445
<211> 414
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(414)
<223> n = A,T,C or G

<400> 445
catgtttatg nttttggatt actttgggca cctagtgttt ctaaatcgtc tatcattctt 60
ttctgttttt caaaagcaga gatggccaga gtctcaacaa actgtatctt caagtctttg 120
tgaaattctt tgcatgtggc agattattgg atgtagtttc ctttaactag catataaatc 180
tggtgtgttt cagataaatg aacagcaaaa tgtggtggaa ttaccatttg gaacattgtg 240
aatgaaaaat tgtgtctcta gattatgtaa caaataacta tttcctaacc attgatcttt 300
ggatttttat aatcctactc acaaatgact aggcttctcc tcttgtattt tgaagcagtg 360
tgggtgctgg attgataaaa aaaaaaaaag tcgacgcggc cgcgaattta gtag 414

<210> 446

<211> 631
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(631)
<223> n = A,T,C or G

<400> 446
acaaattaga anaaagtgcc agagaacacc acataccttg tccggaacat tacaatggct 60
tctgcatgca tgggaagtgt gagcattcta tcaatatgca ggagccatct tgcaggtgtg 120
atgctggtta tactggacaa cactgtgaaa aaaaggacta cagtgttcta tacgttgttc 180
ccggtcctgt acgatttcag tatgtcttaa tcgcagctgt gattggaaca attcagattg 240
ctgtcatctg tgtggtggtc ctctgcatca caagggccaa actttaggta atagcattgg 300
actgagattt gtaaactttc caaccttcca ggaaatgccc cagaagcaac agaattcaca 360
gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tccacgaggt 420
taatctaaag ggagcatgtt tcacagtggc tggactaccg agagcttgga ctacacaata 480
cagtattata gacaaaagaa taagacaaga gatctacaca tgttgccttg catttgtggt 540
aatctacacc aatgaaaaca tgtactacag ctatatttga ttatgtatgg atatatttga 600
aatagtatac attgtcttga tgttttttct g 631

<210> 447
<211> 585
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(585)
<223> n = A,T,C or G

<400> 447
ccttgggaaa antntcacaa tataaagggt cgtagacttt actccaaatt ccaaaaaggt 60
cctggccatg taatcctgaa agttttccca aggtagctat aaaatcctta taagggtgca 120
gcctcttctg gaattcctct gatttcaaag tctcactctc aagttcttga aaacgagggc 180
agttcctgaa aggcaggtat agcaactgat cttcagaaag aggaactgtg tgcaccggga 240
tgggctgcca gagtaggata ggattccaga tgctgacacc ttctgggggga aacagggctg 300
ccaggtttgt catagcactc atcaaagtcc ggtcaacgtc tgtgcttcga atataaacct 360
gttcatgttt ataggactca ttcaagaatt ttctatatct ctttcttata tactctccaa 420
gttcataatg ctgctccatg cccagctggg tgagttggcc aaatccttgt ggccatgagg 480
attcctttat ggggtcagtg ggaaaggtgt caatgggact tcggtctcca tgccgaaaca 540
ccaaagtcac aaacttcaac tccttggcta gtacacttcg gtcta 585

<210> 448
<211> 93
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(93)
<223> n = A,T,C or G

<400> 448
tgctcgtggg tcattctgan nnccgaactg accntgccag ccctgccgan gggccnccat 60
ggctccctag tgccctggag agganggggc tag 93

<210> 449
<211> 706
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(706)
<223> n = A,T,C or G

<400> 449
ccaagttcat gctntgtgct ggacgctgga cagggggcaa aagcnnttgc tcgtgggtca 60
ttctgancac cgaactgacc atgccagccc tgccgatggt cctccatggc tccctagtgc 120
cctggagagg aggtgtctag tcagagagta gtcctggaag gtggcctctg ngaggagcca 180
cggggacagc atcctgcaga tggtcgggcg cgtcccattc gccattcagg ctgcgcaact 240
gttgggaagg gcgatcggtg cgggcctctt cgctattacg ccagctggcg aaagggggat 300
gtgctgcaag gcgattaagt tgggtaacgc cagggttttc ccagtcncga cgttgtaaaa 360
cgacggccag tgaattgaat ttaggtgacn ctatagaaga gctatgacgt cgcatgcacg 420
cgtacgtaag cttggatcct ctagagcggc cgcctactac tactaaattc gcggccgcgt 480
cgacgtggga tccncactga gagagtggag agtgacatgt gctggacnct gtccatgaag 540
cactgagcag aagctggagg cacaacgcnc cagacactca cagctactca ggaggctgag 600
aacaggttga acctgggagg tggaggttgc aatgagctga gatcaggccn ctgcncccca 660
gcatggatga cagagtgaaa ctccatctta aaaaaaaaaa aaaaaa 706

<210> 450
<211> 493
<212> DNA
<213> Homo sapiens

<400> 450
gagacggagt gtcactctgt tgcccaggct ggagtgcagc aagacactgt ctaagaaaaa 60
acagttttaa aaggtaaaac aacataaaaa gaaatatcct atagtggaaa taagagagtc 120
aaatgaggct gagaacttta caaagggatc ttacagacat gtcgccaata tcactgcatg 180
agcctaagta taagaacaac ctttggggag aaaccatcat ttgacagtga ggtacaattc 240
caagtcaggt agtgaaatgg gtggaattaa actcaaatta atcctgccag ctgaaacgca 300
agagacactg tcagagagtt aaaaagtgag ttctatccat gaggtgattc cacagtcttc 360
tcaagtcaac acatctgtga actcacagac caagttctta aaccactgtt caaactctgc 420
tacacatcag aatcacctgg agagctttac aaactcccat tgccgagggt cgacgcggcc 480
gcgaatttag tag 493

<210> 451
<211> 501
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 451
gggcgcgtcc cattcgccat tcaggctgcg caactgttgg gaagggcgat cggtgcgggc 60
ctcttcgcta ttacgccagc tggcgaaagg gggatgtgct gcaaggcgat taagttgggt 120
aacgccaggg ttttcccagt cncgacgttg taaaacgacg gccagtgaat tgaatttagg 180
tgacnctata gaagagctat gacgtcgcat gcacgcgtac gtaagcttgg atcctctaga 240
gcggccgcct actactacta aattcgcggc cgcgtcgacg tgggatccnc actgagagag 300
tggagagtga catgtgctgg acnctgtcca tgaagcactg agcagaagct ggaggcacaa 360
cgcnccagac actcacagct actcaggagg ctgagaacag gttgaacctg ggaggtggag 420

gttgcaatga gctgagatca ggccnctgcn ccccagcatg gatgacagag tgaaactcca 480
tcttaaaaaa aaaaaaaaaa a 501

<210> 452
<211> 51
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(51)
<223> n = A,T,C or G

<400> 452
agacggtttc accnttacaa cncctttag gatgggnntt ggggagcaag c 51

<210> 453
<211> 317
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(317)
<223> n = A,T,C or G

<400> 453
tacatcttgc tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa 60
acatctgaag agctagtcta tcagcatctg gcaagtgaat tggatggttc tcagaaccat 120
ttcacccana cagcctgttt ctatcctgtt taataaatta gtttgggttc tctacatgca 180
taacaaaccc tgctccaatc tgtcacataa aagtctgtga cttgaagttt antcagcacc 240
cccaccaaac tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataagg 300
tacccatgtc tttatta 317

<210> 454
<211> 231
<212> DNA
<213> Homo sapiens

<400> 454
ttcgaggtac aatcaactct cagagtgtag tttccttcta tagatgagtc agcattaata 60
taagccacgc cacgctcttg aaggagtctt gaattctcct ctgctcactc agtagaacca 120
agaagaccaa attcttctgc atcccagctt gcaaacaaaa ttgttcttct aggtctccac 180
ccttcctttt tcagtgttcc aaagctcctc acaatttcat gaacaacagc t 231

<210> 455
<211> 231
<212> DNA
<213> Homo sapiens

<400> 455
taccaaagag ggcataataa tcagtctcac agtagggttc accatcctcc aagtgaaaaa 60
cattgttccg aatgggcttt ccacaggcta cacacacaaa acaggaaaca tgccaagttt 120
gtttcaacgc attgatgact tctccaagga tcttcctttg gcatcgacca cattcagggg 180
caaagaattt ctcatagcac agctcacaat acagggctcc tttctcctct a 231

<210> 456
<211> 231

<212> DNA
<213> Homo sapiens

<400> 456
ttggcaggta cccttacaaa gaagacacca taccttatgc gttattaggt ggaataatca 60
ttccattcag tattatcgtt attattcttg gagaaaccct gtctgtttac tgtaaccttt 120
tgcactcaaa ttcctttatc aggaataact acatagccac tatttacaaa gccattggaa 180
ccttttttatt tggtgcagct gctagtcagt ccctgactga cattgccaag t 231

<210> 457
<211> 231
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(231)
<223> n = A,T,C or G

<400> 457
cgaggtaccc aggggtctga aaatctctnn tttantagtc gatagcaaaa ttgttcatca 60
gcattcctta atatgatctt gctataatta gatttttctc cattagagtt catacagttt 120
tatttgattt tattagcaat ctctttcaga agacccttga gatcattaag ctttgtatcc 180
agttgtctaa atcgatgcct catttcctct gaggtgtcgc tggcttttgt g 231

<210> 458
<211> 231
<212> DNA
<213> Homo sapiens

<400> 458
aggtctggtt ccccccactt ccactcccct ctactctctc taggactggg ctgggccaag 60
agaagagggg tggttaggga agccgttgag acctgaagcc ccaccctcta ccttccttca 120
acaccctaac cttgggtaac agcatttgga attatcattt gggatgagta gaatttccaa 180
ggtcctgggt taggcatttt ggggggccag accccaggag aagaagattc t 231

<210> 459
<211> 231
<212> DNA
<213> Homo sapiens

<400> 459
ggtaccgagg ctcgctgaca cagagaaacc ccaacgcgag gaaaggaatg gccagccaca 60
ccttcgcgaa acctgtggtg gcccaccagt cctaacggga caggacagag agacagagca 120
gccctgcact gttttccctc caccacagcc atcctgtccc tcattggctc tgtgctttcc 180
actatacaca gtcaccgtcc caatgagaaa caagaaggag caccctccac a 231

<210> 460
<211> 231
<212> DNA
<213> Homo sapiens

<400> 460
gcaggtataa catgctgcaa caacagatgt gactaggaac ggccggtgac atggggaggg 60
cctatcaccc tattcttggg ggctgcttct tcacagtgat catgaagcct agcagcaaat 120
cccacctccc cacacgcaca cggccagcct ggagcccaca gaagggtcct cctgcagcca 180
gtggagcttg gtccagcctc cagtccaccc ctaccaggct taaggataga a 231

<210> 461
<211> 231
<212> DNA
<213> Homo sapiens

<400> 461
cgaggtttga gaagctctaa tgtgcagggg agccgagaag caggcggcct agggagggtc 60
gcgtgtgctc cagaagagtg tgtgcatgcc agaggggaaa caggcgcctg tgtgtcctgg 120
gtggggttca gtgaggagtg ggaaattggt tcagcagaac caagccgttg ggtgaataag 180
agggggattc catggcactg atagagccct atagtttcag agctgggaat t 231

<210> 462
<211> 231
<212> DNA
<213> Homo sapiens

<400> 462
aggtaccctc attgtagcca tgggaaaatt gatgttcagt ggggatcagt gaattaaatg 60
gggtcatgca agtataaaaa ttaaaaaaaa aagacttcat gcccaatctc atatgatgtg 120
gaagaactgt tagagagacc aacagggtag tgggttagag atttccagag tcttacattt 180
tctagaggag gtatttaatt tcttctcact catccagtgt tgtatttagg a 231

<210> 463
<211> 231
<212> DNA
<213> Homo sapiens

<400> 463
tactccagcc tggtgacaga gcgagaccct atcaccgccc cccaccccac caaaaaaaaa 60
actgagtaga caggtgtcct cttggcatgg taagtcttaa gtcccctccc agatctgtga 120
catttgacag gtgtcttttc ctctggacct cggtgtcccc atctgagtga gaaaaggcag 180
tggggaggtg gatcttccag tcgaagcggt atagaagccc gtgtgaaaag c 231

<210> 464
<211> 231
<212> DNA
<213> Homo sapiens

<400> 464
gtactctaag attttatcta agttgccttt tctgggtggg aaagtttaac cttagtgact 60
aaggacatca catatgaaga atgtttaagt tggaggtggc aacgtgaatt gcaaacaggg 120
cctgcttcag tgactgtgtg cctgtagtcc cagctactcg ggagtctgtg tgaggccagg 180
ggtgccagcg caccagctag atgctctgta acttctaggc cccattttcc c 231

<210> 465
<211> 231
<212> DNA
<213> Homo sapiens

<400> 465
catgttgttg tagctgtggt aatgctggct gcatctcaga cagggttaac ttcagctcct 60
gtggcaaatt agcaacaaat tctgacatca tatttatggt ttctgtatct ttgttgatga 120
aggatggcac aatttttgct tgtgttcata atatactcag attagttcag ctccatcaga 180
taaactggag acatgcagga cattagggta gtgttgtagc tctggtaatg a 231

<210> 466
<211> 231
<212> DNA

<213> Homo sapiens

<400> 466
caggtacctc tttccattgg atactgtgct agcaagcatg ctctccgggg tttttttaat 60
ggccttcgaa cagaacttgc cacataccca ggtataatag tttctaacat ttgcccagga 120
cctgtgcaat caaatattgt ggagaattcc ctagctggag aagtcacaaa gactataggc 180
aataatggag accagtccca caagatgaca accagtcgtt gtgtgcggct g 231

<210> 467
<211> 311
<212> DNA
<213> Homo sapiens

<400> 467
gtacaccctg gcacagtcca atctgaactg gttcggcact catctttcat gagatggatg 60
tggtggcttt tctccttttt catcaagact cctcagcagg gagcccagac cagcctgcac 120
tgtgccttaa cagaaggtct tgagattcta agtgggaatc atttcagtga ctgtcatgtg 180
gcatgggtct ctgcccaagc tcgtaatgag actatagcaa ggcggctgtg ggacgtcagt 240
tgtgacctgc tgggcctccc aatagactaa caggcagtgc cagttggacc caagagaaga 300
ctgcagcaga c 311

<210> 468
<211> 3112
<212> DNA
<213> Homo sapiens

<400> 468
cattgtgttg ggagaaaaac agaggggaga tttgtgtggc tgcagccgag ggagaccagg 60
aagatctgca tggtgggaag gacctgatga tacagagttt gataggagac aattaaaggc 120
tggaaggcac tggatgcctg atgatgaagt ggactttcaa actggggcac tactgaaacg 180
atgggatggc cagagacaca ggagatgagt tggagcaagc tcaataacaa agtggttcaa 240
cgaggacttg gaattgcatg gagctggagc tgaagtttag cccaattgtt tactagttga 300
gtgaatgtgg atgattggat gatcatttct catctctgag cctcaggttc cccatccata 360
aaatgggata cacagtatga tctataaagt gggatatagt atgatctact tcactgggtt 420
atttgaagga tgaattgaga taatttattt caggtgccta gaacaatgcc cagattagta 480
catttggtgg aactgagaaa tggcataaca ccaaatttaa tatatgtcag atgttactat 540
gattatcatt caatctcata gttttgtcat ggcccaattt atcctcactt gtgcctcaac 600
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tttccattcc agttggcttc ttgggtttgc tagctgcatc actagtcatc ttaaataaat 720
gaagttttaa catttctcca gtgatttttt tatctcacct ttgaagatac tatgttatgt 780
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aaagtgagca ttaccaatga gaggaaaaca gacgagaaaa tcttgatggc ttcacaagac 1740
atgcaacaaa caaaatggaa tactgtgatg acatgaggca gccaagctgg ggaggagata 1800
accacggggc agagggtcag gattctggcc ctgctgccta aactgtgcgt tcataaccaa 1860

atcatttcat atttctaacc ctcaaaacaa agctgttgta atatctgatc tctacggttc 1920
cttctgggcc caacattctc catatatcca gccacactca tttttaatat ttagttccca 1980
gatctgtact gtgacctttc tacactgtag aataacatta ctcattttgt tcaaagaccc 2040
ttcgtgttgc tgcctaatat gtagctgact gtttttccta aggagtgttc tggcccaggg 2100
gatctgtgaa caggctggga agcatctcaa gatctttcca gggttatact tactagcaca 2160
cagcatgatc attacggagt gaattatcta atcaacatca tcctcagtgt ctttgcccat 2220
actgaaattc atttcccact tttgtgccca ttctcaagac ctcaaaatgt cattccatta 2280
atatcacagg attaactttt ttttttaacc tggaagaatt caatgttaca tgcagctatg 2340
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ctttgtttga ttttttttcc agtataaagt taaaatgctt agccttgtac tgaggctgta 2460
tacagccaca gcctctcccc atccctccag ccttatctgt catcaccatc aacccctccc 2520
atgcacctaa acaaaatcta acttgtaatt ccttgaacat gtcaggcata cattattcct 2580
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ttgactatct tacttcatgc aaagaaggga cacatatgag attcatcatc acatgagaca 2700
gcaaatacta aaagtgtaat ttgattataa gagtttagat aaatatatga aatgcaagag 2760
ccacagaggg aatgtttatg gggcacgttt gtaagcctgg gatgtgaagc aaaggcaggg 2820
aacctcatag tatcttatat aatatacttc atttctctat ctctatcaca atatccaaca 2880
agcttttcac agaattcatg cagtgcaaat ccccaaaggt aacctttatc catttcatgg 2940
tgagtgcgct ttagaatttt ggcaaatcat actggtcact tatctcaact ttgagatgtg 3000
tttgtccttg tagttaattg aaagaaatag ggcactcttg tgagccactt tagggttcac 3060
tcctggcaat aaagaattta caaagagcaa aaaaaaaaaa aaaaaaaaaa aa 3112

<210> 469
<211> 2229
<212> DNA
<213> Homo sapiens

<400> 469
agctctttgt aaattcttta ttgccaggag tgaaccctaa agtggctcac aagagtgccc 60
tatttctttc aattaactac aaggacaaac acatctcaaa gttgagataa gtgaccagta 120
tgatttgcca aaattctaaa gcgcactcac catgaaatgg ataaaggtta cctttgggga 180
tttgcactgc atgaattctg tgaaaagctt gttggatatt gtgatagaga tagagaaatg 240
aagtatatta tataagatac tatgaggttc cctgcctttg cttcacatcc caggcttaca 300
aacgtgcccc ataaacattc cctctgtggc tcttgcattt catatattta tctaaactct 360
tataatcaaa tacactttta gtatttgctg tctcatgtga tgatgaatct catatgtgtc 420
ccttctttgc atgaagtaag atagtcaact tattcaaaac tttacatcat tctagattta 480
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<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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<210> 476
<211> 3434
<212> DNA
<213> Homo sapiens

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<210> 477
<211> 140
<212> PRT
<213> Homo sapiens

<400> 477
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His Tyr His Arg Asp Thr Asp Thr Arg Arg His His His Met Asp Thr
            20                  25                  30

Leu Ser His Tyr His Arg Asp Thr Arg His His Thr Val Thr Trp Thr
        35                  40                  45

His His His Thr His Glu His Thr Asp Thr Leu Pro Tyr Gly His Trp
    50                  55                  60

His Thr His Cys His Thr Val Thr Trp Thr His Leu His Thr Ile Thr
65                  70                  75                  80

Pro Pro His Thr Leu Pro Val Asp Thr Arg Thr His Arg His Cys His
                85                  90                  95

Thr Asp Thr Gln Asn Thr Val Thr Arg Arg His His His Ala Asp Thr
            100                 105                 110

Pro Pro Leu Trp Cys Arg Leu Asn Tyr Pro Ala Gly Gly Thr Ala Val
        115                 120                 125

Ala Tyr Ser Cys Leu Ser Asp Trp Leu Ser Pro Gln
    130                 135                 140


<210> 478
<211> 143
<212> PRT
<213> Homo sapiens

<400> 478
Met Tyr Arg His Thr Glu Thr Leu Pro His Gly Asp Thr Val Thr Gln
                5                   10                  15

Ser His Gly His Thr Gly Ile Val Thr Trp Thr Asp Thr Gln Thr Tyr
            20                  25                  30

Gly Glu Ile Thr Trp Thr His His His Thr Ile Thr Gly Thr Gln Thr
        35                  40                  45

His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr
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50 55 60

Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr
65 70 75 80

Pro Thr His Cys His Met Asp Thr Gly Thr His Thr Ala Thr Leu Ser
85 90 95

His Gly His Thr Ser Thr Pro Ser His His His Thr His Cys Leu Trp
100 105 110

Thr Gln Gly His Thr Asp Thr Val Thr Gln Ile His Lys Thr Leu Ser
115 120 125

His Gly Asp Ile Thr Met Gln Ile His His His Ser Gly Ala Val
130 135 140

<210> 479
<211> 222
<212> PRT
<213> Homo sapiens

<400> 479
Met Tyr Arg His Thr Glu Thr Leu Pro His Gly Asp Thr Val Thr Gln
5 10 15

Ser His Glu His Thr Gly Ile Val Thr Trp Thr Asp Thr Gln Thr Tyr
20 25 30

Gly Glu Ile Thr Leu Thr His His His Thr Ile Thr Gly Thr Gln Thr
35 40 45

His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr
50 55 60

Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr
65 70 75 80

Pro Thr His Cys His Met Asp Thr Ala Thr His Thr Ala Thr Leu Ser
85 90 95

His Gly His Thr Ser Ile Pro Ser His His His Thr His Cys His Val
100 105 110

Asp Thr Arg Thr His Arg His Cys His Thr Asp Thr Gln Asn Thr Val
115 120 125

Thr Arg Arg His His His Ala Asp Thr Pro Pro His Gly His Ser Thr
130 135 140

Arg His Ser Ala Thr Gln Ile His His His Thr Glu Met Arg Thr His
145 150 155 160

Cys His Thr Asp Thr Thr Thr Ser Leu Pro His Phe His Val Ser Ala
165 170 175

Gly Gly Val Gly Pro Thr Thr Leu Gly Ser Asn Arg Glu Ile Thr Trp

180 185 190

Thr Tyr Ser Glu Gly Lys Ile Phe Phe Tyr Phe Leu Gly Asn Gln Ala
195 200 205

Arg Leu Cys Leu Lys Lys Arg Lys Lys Lys Gln Tyr Thr Val
210 215 220

<210> 480
<211> 144
<212> PRT
<213> Homo sapiens

<400> 480
Met Glu Pro Tyr Arg Gly Asn Glu Gln Pro Ser Gln Glu Gln Gly Val
5 10 15

Cys Cys Leu Trp Gly Leu Gln Ser Leu Pro Gln Gly Ser Tyr Val Thr
20 25 30

Val Gly Phe Leu Val Val Lys Arg Gln Thr Ile Gly Arg Leu Glu Arg
35 40 45

Asp Phe Met Phe Lys Cys Arg Lys Gln Pro Gly Leu Pro Pro Ser Gly
50 55 60

Leu Cys Leu Leu Trp Pro Trp Pro Asn Leu Glu Phe Gly Arg Arg Gln
65 70 75 80

Asp Arg Leu Thr Trp Ser Ser Val Ser Val Ala Gly Val Cys Ala Cys
85 90 95

Arg Ala Arg Pro Gly Trp Leu Gly Glu Gln Pro Ala Thr Ser Ala Gly
100 105 110

Val Arg Leu Glu Gln Val Glu Gln Pro Pro Ala His Pro Leu Gln Glu
115 120 125

Ala Gly Val Ala Arg Phe Pro Arg Pro Glu Trp Val Pro Pro Asn Gly
130 135 140

<210> 481
<211> 167
<212> PRT
<213> Homo sapiens

<400> 481
Met His Gly Pro Gln Val Leu Ala Arg Cys Ser Glu Cys Ala Cys Pro
5 10 15

Ala Leu Ala Ala Thr Ser Ala Gly Val Arg Leu Glu Gly Val Asp Arg
20 25 30

Pro Pro Thr Leu Pro Ser Gln Gly Ser Gly Trp Pro Cys Ser His Ser
35 40 45

Leu Ser Gly Cys His Leu Met Ala Asp Gly Ala Lys Ala Leu Gly Lys
50 55 60

Ala Asp Gly Pro Trp Pro Tyr Leu Phe Val Arg Arg Thr Asp Val Pro
65 70 75 80

Cys Pro Ala Ala Ser Glu Val Gly Gly Cys Ala Pro Ser Ser Trp Arg
85 90 95

Ala Leu Ala Glu Val Thr Gly Cys Ser Leu Gly Pro Leu Gly Leu Ala
100 105 110

Gln His Ala Gln Ala Ser Val Leu Leu Leu Cys Tyr Lys Trp Ser His
115 120 125

Ile Gly Glu Thr Ser Ser His Leu Arg Ser Lys Val Tyr Ala Ala Phe
130 135 140

Gly Gly Ser Ser Pro Cys Leu Lys Gly Leu Met Ser Leu Trp Ala Ser
145 150 155 160

Trp Leu Ser Arg Gly Arg Pro
165

<210> 482
<211> 143
<212> PRT
<213> Homo sapiens

<400> 482
Met Glu Pro Tyr Arg Gly Asn Lys Lys Gln Val Gln Glu Lys Gly Val
5 10 15

Pro Cys Leu Trp Gly Ser Ser Pro Cys Leu Arg Cys His Met Ala Leu
20 25 30

Arg Ala Ser Trp Leu Pro Gly Gly Gly Pro Gln Ala Ile Leu Gly Arg
35 40 45

Thr Leu Cys Ser Ser Ala Glu Ser Ser Gln Asp Cys His Pro Gly Gly
50 55 60

Pro Ser Ile Ala Leu Ala Lys Pro Cys Arg Gly Val Trp Leu Leu Phe
65 70 75 80

Glu Pro Ala Trp Pro Pro Trp His Ala Arg Ala Pro Gly Ala Gly Thr
85 90 95

Leu Leu Arg Val Cys Leu Ser Cys Leu Gly Cys His Leu Cys Gly Gly
100 105 110

Ala Ser Gly Gly Gly Gly Pro Ala Thr Asn Leu Thr Gln Ser Arg Lys
115 120 125

Trp Met Ala Met Phe Pro Gln Pro Glu Trp Leu Pro Pro Asp Gly
130 135 140

<210> 483
<211> 143
<212> PRT
<213> Homo sapiens

<400> 483
Met Glu Thr Gln Arg Gly Asn Lys Gln Arg Ala Gln Glu Gln Gly Val
5 10 15

Cys Cys Leu Trp Gly Ser Ser Pro Cys Leu Gly Ser Tyr Gly Thr Ala
20 25 30

Gly Phe Leu Val Ala Lys Arg Arg Thr Thr Gly Leu Leu Glu Glu Asp
35 40 45

Phe Thr Phe Lys Cys Arg Lys Gln Pro Lys Leu Pro Ser Met Arg Leu
50 55 60

Ser Leu Leu Trp Pro Trp Arg Asp Leu Lys Phe Val Pro Arg Gln Asp
65 70 75 80

Lys Leu Thr Arg Ser Ser Val Ser Val Ala Gly Ala Tyr Ala Cys Arg
85 90 95

Ala Gly Pro Gly Trp Leu Lys Glu Gln Pro Ala Thr Ser Ala Arg Val
100 105 110

Arg Leu Val Gln Ala Glu His Pro Pro Pro His Pro Leu Glu Glu Val
115 120 125

Gly Met Ala Arg Phe Pro Gln Pro Glu Cys Leu Pro Pro Tyr Cys
130 135 140

<210> 484
<211> 30
<212> PRT
<213> Homo Sapien

<400> 484
Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
1 5 10 15
Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile
20 25 30

<210> 485
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 485
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<210> 486
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 486
gcgaattctc acgctgagta tttggcc 27

<210> 487
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 487
cccgaattct tagctgccca tccgaacgcc ttcatc 36

<210> 488
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 488
gggaagcttc ttccccggct gcaccagctg tgc 33

<210> 489
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 489
Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg Ala Val Tyr Leu Ala
1 5 10 15
Ser Val Ala

<210> 490
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 490
Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala Thr Cys

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Leu Ser His Ser
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      <210> 491
      <211> 20
      <212> PRT
      <213> Artificial Sequence

      <220>
      <223> Made in a lab

      <400> 491
Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu
 1               5                   10                  15
Thr Gly Phe Thr
            20

      <210> 492
      <211> 20
      <212> PRT
      <213> Artificial Sequence

      <220>
      <223> Made in a lab

      <400> 492
Ala Leu Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr
 1               5                   10                  15
Leu Ala Ser Leu
            20

      <210> 493
      <211> 20
      <212> PRT
      <213> Artificial Sequence

      <220>
      <223> Made in a lab

      <400> 493
Tyr Thr Leu Ala Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro
 1               5                   10                  15
Lys Tyr Arg Gly
            20

      <210> 494
      <211> 20
      <212> PRT
      <213> Artificial Sequence

      <220>
      <223> Made in a lab

      <400> 494
Leu Pro Lys Tyr Arg Gly Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser
 1               5                   10                  15
Leu Met Ile Ser
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20

<210> 495
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 495
Asp Ser Leu Met Thr Ser Phe Leu Pro Gly Pro Lys Pro Gly Ala Pro
1 5 10 15
Phe Pro Asn Gly
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<210> 496
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 496
Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu
1 5 10 15
Pro Pro Pro Pro Ala
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<210> 497
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 497
Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser Ala Cys Asp Val
1 5 10 15
Ser Val Arg Val
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<210> 498
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 498
Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala Arg Val
1 5 10 15
Val Pro Gly Arg
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<210> 499
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 499
Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp
1 5 10 15
Ser Ala Phe Leu
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<210> 500
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 500
Leu Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met
1 5 10 15
Gly Ser Ile Val
20

<210> 501
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 501
Phe Met Gly Ser Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met
1 5 10 15
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<210> 502
<211> 414
<212> DNA
<213> Homo Sapien

<220>
<221> misc_feature
<222> (1)...(414)
<223> n=A,T,C or G

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ctgtagagtt tttggaatng acctcagtag caatgcaatg agctgggtcc gccaggctcc 180
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gaaaggccga ttnatnattt ccaaaacctn gaccacggtg gatttgaaaa tgaccagtcc 300
gacaaccgag gacacggcca cctattttg tggcagaatg aatactggta atagtggttg 360
gaagaatatt tggggcccag gcaccctggt caccgtntcc tcagggcaac ctaa 414

<210> 503
<211> 379
<212> DNA
<213> Homo Sapien

<220>
<221> misc_feature
<222> (1)...(379)
<223> n=A,T,C or G

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tntccttagg gcaacctaa 379

<210> 504
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 504
Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro Tyr Phe Lys Glu
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Asn Ser Ala

<210> 505
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 505
Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn Asp Asn Val Thr
1 5 10 15
Asn Thr Ala Asn
20

<210> 506
<211> 407
<212> DNA
<213> Homo Sapien

<400> 506

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<210> 507
<211> 422
<212> DNA
<213> Homo Sapien

<400> 507
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<210> 508
<211> 411
<212> DNA
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<220>
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<222> (1)...(411)
<223> n=A,T,C or G

<400> 508
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cggtggagga gtccgggggt cgcctggtca cgcctgggac acccctgaca ctcacctgca 120
cagtctctgg aatcgacctc agtagctact gcatgagctg ggtccgccag gctccaggga 180
aggggctgga atggatcgga atcattggta ctcctggtga cacatactac gcgaggtggg 240
cgaaaggccg attcaccatc tccaaaacct cgaccacggt gcatntgaaa atcnccagtc 300
cgacaaccga ggacacggcc acctatttct gtgccagaga tcttcgggat ggtagtagta 360
ctggttatta taaaatctgg ggcccaggca ccctggtcac cgtctccttg g 411

<210> 509
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 509
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
1 5 10 15

<210> 510
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 510
Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile
1 5 10 15

<210> 511
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 511

Tyr His Pro Ser Met Phe Cys Ala Gly Gly Gly Gln Asp Gln Lys
1 5 10 15

<210> 512
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 512
Asp Ser Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu
1 5 10 15

<210> 513
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 513
Ala Pro Cys Gly Gln Val Gly Val Pro Asx Val Tyr Thr Asn Leu
1 5 10 15

<210> 514
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 514
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
1 5 10 15

<210> 515

<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 515
Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg
1 5 10 15

<210> 516
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 516
Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln
1 5 10 15

<210> 517
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 517
Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met
1 5 10 15

<210> 518
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 518
Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly
1 5 10 15

<210> 519
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 519
Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg Asn Tyr Asp Glu Gly Cys
1 5 10 15

Gly

<210> 520
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 520
Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr
1 5 10 15
Glu Ala Arg Arg His Tyr Asp Glu Gly
20 25

<210> 521
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 521
Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu
1 5 10 15
Pro Pro Pro Pro Ala
20

<210> 522
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 522
Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr Gly Ser Gln Glu Asp
1 5 10 15
Phe Thr Gln Val
20

<210> 523
<211> 254
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<220>
<221> VARIANT
<222> (1)...(254)
<223> Xaa = any amino acid

<400> 523

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Leu Gly Val Ala Gly Ser Leu Val Ser Gly Ser Cys Ser Gln Ile Ile
            20                  25                  30
Asn Gly Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu
        35                  40                  45
Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln
    50                  55                  60
Trp Val Leu Ser Ala Thr His Cys Phe Gln Asn Ser Tyr Thr Ile Gly
65                  70                  75                  80
Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met
                85                  90                  95
Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu
            100                 105                 110
Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu
        115                 120                 125
Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala
    130                 135                 140
Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg
145                 150                 155                 160
Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu
                165                 170                 175
Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys
            180                 185                 190
Ala Gly Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser Gly
        195                 200                 205
Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly
    210                 215                 220
Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu
225                 230                 235                 240
Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
                245                 250
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<210> 524
<211> 765
<212> DNA
<213> Homo sapien

<400> 524

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tcgcagccct ggcaggcggc actggtcatg gaaaacgaat tgttctgctc gggcgtcctg     180
gtgcatccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggg     240
ctgggcctgc acagtcttga ggccgaccaa gagccaggga gccagatggt ggaggccagc     300
ctctccgtac ggcacccaga gtacaacaga cccttgctcg ctaacgacct catgctcatc     360
aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag     420
tgccctaccg cggggaactc ttgcctcgtt tctggctggg gtctgctggc gaacggcaga     480
atgcctaccg tgctgcagtg cgtgaacgtg tcggtggtgt ctgaggaggt ctgcagtaag     540
ctctatgacc cgctgtacca ccccagcatg ttctgcgccg gcggagggca agaccagaag     600
gactcctgca acggtgactc tgggggggccc ctgatctgca acgggtactt gcagggcctt     660
gtgtctttcg gaaaagcccc gtgtggccaa gttggcgtgc caggtgtcta caccaacctc     720
tgcaaattca ctgagtggat agagaaaacc gtccaggcca gttaa                     765
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<210> 525
<211> 254
<212> PRT
<213> Homo sapien

<400> 525
Met Ala Thr Ala Gly Asn Pro Trp Gly Trp Phe Leu Gly Tyr Leu Ile
1 5 10 15
Leu Gly Val Ala Gly Ser Leu Val Ser Gly Ser Cys Ser Gln Ile Ile
20 25 30
Asn Gly Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu
35 40 45
Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln
50 55 60
Trp Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly
65 70 75 80
Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met
85 90 95
Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu
100 105 110
Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu
115 120 125
Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala
130 135 140
Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg
145 150 155 160
Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu
165 170 175
Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys
180 185 190
Ala Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly
195 200 205
Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly
210 215 220
Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu
225 230 235 240
Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
245 250

<210> 526
<211> 963
<212> DNA
<213> Homo sapiens

<400> 526
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aaagcccatt tctgggttgg cttcccccctc ctttccatgt atgtagtggc aatgtttgga 120
aactgcatcg tggtcttcat cgtaaggacg gaacgcagcc tgcacgctcc gatgtacctc 180
tttctctgca tgcttgcagc cattgacctg gccttatcca catccaccat gcctaagatc 240
cttgcccttt tctggtttga ttcccgagag attagctttg aggcctgtct tacccagatg 300
ttctttattc atgccctctc agccattgaa tccaccatcc tgctggccat ggcctttgac 360
cgttatgtgg ccatctgcca cccactgcgc catgctgcag tgctcaacaa tacagtaaca 420
gcccagattg gcatcgtggc tgtggtccgc ggatccctct ttttttccc actgcctctg 480
ctgatcaagc ggctggcctt ctgccactcc aatgtcctct cgcactccta ttgtgtccac 540
caggatgtaa tgaagttggc ctatgcagac actttgccca atgtggtata tggtcttact 600
gccattctgc tggtcatggg cgtggacgta atgttcatct ccttgtccta ttttctgata 660
atacgaacgg ttctgcaact gccttccaag tcagagcggg ccaaggcctt tggaacctgt 720
gtgtcacaca ttggtgtggt actcgccttc tatgtgccac ttattggcct ctcagttgta 780
caccgctttg gaaacagcct tcatcccatt gtgcgtgttg tcatgggtga catctacctg 840
ctgctgcctc ctgtcatcaa tcccatcatc tatggtgcca aaaccaaaca gatcagaaca 900
cgggtgctgg ctatgttcaa gatcagctgt gacaaggact tgcaggctgt gggaggcaag 960
tga 963

<210> 527
<211> 320
<212> PRT
<213> Homo sapiens

<400> 527
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Met Ser Ser Cys Asn Phe Thr His Ala Thr Phe Val Leu Ile Gly Ile
                5                   10                  15

Pro Gly Leu Glu Lys Ala His Phe Trp Val Gly Phe Pro Leu Leu Ser
            20                  25                  30

Met Tyr Val Val Ala Met Phe Gly Asn Cys Ile Val Val Phe Ile Val
        35                  40                  45

Arg Thr Glu Arg Ser Leu His Ala Pro Met Tyr Leu Phe Leu Cys Met
    50                  55                  60

Leu Ala Ala Ile Asp Leu Ala Leu Ser Thr Ser Thr Met Pro Lys Ile
65                  70                  75                  80

Leu Ala Leu Phe Trp Phe Asp Ser Arg Glu Ile Ser Phe Glu Ala Cys
                85                  90                  95

Leu Thr Gln Met Phe Phe Ile His Ala Leu Ser Ala Ile Glu Ser Thr
            100                 105                 110

Ile Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala Ile Cys His Pro
        115                 120                 125

Leu Arg His Ala Ala Val Leu Asn Asn Thr Val Thr Ala Gln Ile Gly
    130                 135                 140

Ile Val Ala Val Val Arg Gly Ser Leu Phe Phe Phe Pro Leu Pro Leu
145                 150                 155                 160

Leu Ile Lys Arg Leu Ala Phe Cys His Ser Asn Val Leu Ser His Ser
                165                 170                 175

Tyr Cys Val His Gln Asp Val Met Lys Leu Ala Tyr Ala Asp Thr Leu
            180                 185                 190

Pro Asn Val Val Tyr Gly Leu Thr Ala Ile Leu Leu Val Met Gly Val
        195                 200                 205

Asp Val Met Phe Ile Ser Leu Ser Tyr Phe Leu Ile Ile Arg Thr Val
    210                 215                 220

Leu Gln Leu Pro Ser Lys Ser Glu Arg Ala Lys Ala Phe Gly Thr Cys
225                 230                 235                 240

Val Ser His Ile Gly Val Val Leu Ala Phe Tyr Val Pro Leu Ile Gly
                245                 250                 255

Leu Ser Val Val His Arg Phe Gly Asn Ser Leu His Pro Ile Val Arg
            260                 265                 270
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Val Val Met Gly Asp Ile Tyr Leu Leu Leu Pro Pro Val Ile Asn Pro
275 280 285

Ile Ile Tyr Gly Ala Lys Thr Lys Gln Ile Arg Thr Arg Val Leu Ala
290 295 300

Met Phe Lys Ile Ser Cys Asp Lys Asp Leu Gln Ala Val Gly Gly Lys
305 310 315 320

<210> 528
<211> 20
<212> DNA
<213> Homo Sapien

<400> 528
actatggtcc agaggctgtg 20

<210> 529
<211> 20
<212> DNA
<213> Homo Sapien

<400> 529
atcacctatg tgccgcctct 20

<210> 530
<211> 1852
<212> DNA
<213> Homo sapiens

<400> 530
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aaaaccacct atgacaagcc cacagccaac ataatactaa atggggaaaa gttagaagca 120
tttcctctga gaactgcaac aataaataca aggatgctgg attttgtcaa atgccttttc 180
tgtgtctgtt gagatgctta tgtgactttg cttttaattc tgtttatgtg attatcacat 240
ttattgactt gcctgtgtta gaccggaaga gctggggtgt ttctcaggag ccaccgtgtg 300
ctgcggcagc ttcgggataa cttgaggctg catcactggg gaagaaacac aytcctgtcc 360
gtggcgctga tggctgagga cagagcttca gtgtggcttc tctgcgactg gcttcttcgg 420
ggagttcttc cttcatagtt catccatatg gctccagagg aaaattatat tattttgtta 480
tggatgaaga gtattacgtt gtgcagatat actgcagtgt cttcatctct tgatgtgtga 540
ttgggtaggt tccaccatgt tgccgcagat gacatgattt cagtacctgt gtctggctga 600
aaagtgtttg tttgtgaatg gatattgtgg tttctggatc tcatcctctg tgggtggaca 660
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aacgtggtcg cttggggaga ctacgatgac agcgccttca tggatcccag gtaccacgtc 960
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gatctcatcg tcatgctcag ggacacggat gtgaacaaga gggacaagca aaagaggact 1080
gctctacatc tggcctctgc caatgggaat tcagaagtag taaaactcgt gctggacaga 1140
cgatgtcaac ttaatgtcct tgacaacaaa aagaggacag ctctgacaaa ggccgtacaa 1200
tgccaggaag atgaatgtgc gttaatgttg ctggaacatg gcactgatcc aaatattcca 1260
gatgagtatg gaaataccac tctacactat gctgtctaca atgaagataa attaatggcc 1320
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ctgctacttg gtatacatga gcaaaaacag caagtggtga aatttttaat caagaaaaaa 1440
gcgaatttaa atgcgctgga tagatatgga agaactgctc tcatacttgc tgtatgttgt 1500
ggatcagcaa gtatagtcag ccctctactt gagcaaaatg ttgatgtatc ttctcaagat 1560
ctggaaagac ggccagagag tatgctgttt ctagtcatca tcatgtaatt tgccagttac 1620

tttctgacta caaagaaaaa cagatgttaa aaatctcttc tgaaaacagc aatccagaac 1680
aagacttaaa gctgacatca gaggaagagt cacaaaggct taaaggaagt gaaaacagcc 1740
agccagagct agaagattta tggctattga agaagaatga agaacacgga agtactcatg 1800
tgggattccc agaaaacctg actaacggtg ccgctgctgg caatggtgat ga 1852

<210> 531
<211> 879
<212> DNA
<213> Homo sapiens

<400> 531
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aacgtgggca cttctggaga ccacaacgac tcctctgtga agacgcttgg gagcaagagg 120
tgcaagtggt gctgccactg cttcccctgc tgcagggga gcggcaagag caacgtggtc 180
gcttggggag actacgatga cagcgccttc atggatccca ggtaccacgt ccatggagaa 240
gatctggaca agctccacag agctgcctgg tggggtaaag tccccagaaa ggatctcatc 300
gtcatgctca gggacacgga tgtgaacaag agggacaagc aaaagaggac tgctctacat 360
ctggcctctg ccaatgggaa ttcagaagta gtaaaactcg tgctggacag acgatgtcaa 420
cttaatgtcc ttgacaacaa aaagaggaca gctctgacaa aggccgtaca atgccaggaa 480
gatgaatgtg cgttaatgtt gctggaacat ggcactgatc caaatattcc agatgagtat 540
ggaaatacca ctctacacta tgctgtctac aatgaagata aattaatggc caaagcactg 600
ctcttatacg gtgctgatat cgaatcaaaa aacaagcatg gcctcacacc actgctactt 660
ggtatacatg agcaaaaaca gcaagtggtg aaatttttaa tcaagaaaaa agcgaattta 720
aatgcgctgg atagatatgg aagaactgct ctcatacttg ctgtatgttg tggatcagca 780
agtatagtca gccctctact tgagcaaaat gttgatgtat cttctcaaga tctggaaaga 840
cggccagaga gtatgctgtt tctagtcatc atcatgtaa 879

<210> 532
<211> 292
<212> PRT
<213> Homo sapiens

<400> 532
Met His Leu Ser Phe Pro Ala Phe Leu Pro Pro Trp Met Asp Arg Gly
5 10 15

Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp His Asn Asp Ser Ser
20 25 30

Val Lys Thr Leu Gly Ser Lys Arg Cys Lys Trp Cys Cys His Cys Phe
35 40 45

Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val Val Ala Trp Gly Asp
50 55 60

Tyr Asp Asp Ser Ala Phe Met Asp Pro Arg Tyr His Val His Gly Glu
65 70 75 80

Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val Pro Arg
85 90 95

Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Arg Asp
100 105 110

Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser
115 120 125

Glu Val Val Lys Leu Val Leu Asp Arg Arg Cys Gln Leu Asn Val Leu

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    130                 135                 140

Asp Asn Lys Lys Arg Thr Ala Leu Thr Lys Ala Val Gln Cys Gln Glu
145                 150                 155                 160

Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile
                165                 170                 175

Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Val Tyr Asn Glu
            180                 185                 190

Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu
        195                 200                 205

Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Ile His Glu
    210                 215                 220

Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu
225                 230                 235                 240

Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys
                245                 250                 255

Cys Gly Ser Ala Ser Ile Val Ser Pro Leu Leu Glu Gln Asn Val Asp
            260                 265                 270

Val Ser Ser Gln Asp Leu Glu Arg Arg Pro Glu Ser Met Leu Phe Leu
        275                 280                 285

Val Ile Ile Met
    290
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<210> 533
<211> 801
<212> DNA
<213> Homo sapiens

<400> 533

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tatgccactg cacgattctt ggttgccaag aggccaacca caggccatct tgagaaggag 180
tttatgttcc actgcagaaa gcagccagga tcaccatcca ggggacttgg tcttctgtgg 240
ccctggccag acatagaatt tgtgccaagg caggacaagc tcactcagag cagcgtgtta 300
gtacctcaaa tctgtgcgtg ccagacaagg ccaaactggc tcaatgagca accagccacc 360
tctgcagggg tgcgtctgga ggaggtggac cagccaccaa ccttacccag tcaaggaagt 420
ggatggccat gttcccacag cctgagtggc tgccacctga tggctgatat agcaaaggcc 480
ttaggaaaag cagatggccc ttggccctac ctttttgtta gaagaactga tgttccatgt 540
cctgcagcga gtgaggttgg tggctgtgcc cccagctcct ggcacaccct cgcagaggtg 600
actggttgct ctttgagccc tcttagcctt gcccagcatg cacaagcctc agtgctacta 660
ctgtgctaca aatggagcca tataggggaa acgagcagcc atctcaggag caaggtgtat 720
gctgcctttg gggctccag tccttgcctc aagggtctta tgtcactgtg ggcttcttgg 780
ttgccaagag gcagaccata g                                          801
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<210> 534
<211> 266
<212> PRT
<213> Homo sapiens

<400> 534

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Met Tyr Lys Leu Gln Cys Asn Asn Cys Ala Thr Asn Gly Ala Thr Glu
                5                   10                  15

Arg Lys Gln Ala Ala Gly Ser Gly Ala Gly Tyr Ala Leu Pro Ser Ala
            20                  25                  30

Leu Gln Ser Met Pro Gln Gly Ser Tyr Ala Thr Ala Arg Phe Leu Val
        35                  40                  45

Ala Lys Arg Pro Thr Thr Gly His Leu Glu Lys Glu Phe Met Phe His
    50                  55                  60

Cys Arg Lys Gln Pro Gly Ser Pro Ser Arg Gly Leu Gly Leu Leu Trp
65                  70                  75                  80

Pro Trp Pro Asp Ile Glu Phe Val Pro Arg Gln Asp Lys Leu Thr Gln
                85                  90                  95

Ser Ser Val Leu Val Pro Gln Ile Cys Ala Cys Gln Thr Arg Pro Asn
            100                 105                 110

Trp Leu Asn Glu Gln Pro Ala Thr Ser Ala Gly Val Arg Leu Glu Glu
        115                 120                 125

Val Asp Gln Pro Pro Thr Leu Pro Ser Gln Gly Ser Gly Trp Pro Cys
    130                 135                 140

Ser His Ser Leu Ser Gly Cys His Leu Met Ala Asp Ile Ala Lys Ala
145                 150                 155                 160

Leu Gly Lys Ala Asp Gly Pro Trp Pro Tyr Leu Phe Val Arg Arg Thr
                165                 170                 175

Asp Val Pro Cys Pro Ala Ala Ser Glu Val Gly Gly Cys Ala Pro Ser
            180                 185                 190

Ser Trp His Thr Leu Ala Glu Val Thr Gly Cys Ser Leu Ser Pro Leu
        195                 200                 205

Ser Leu Ala Gln His Ala Gln Ala Ser Val Leu Leu Leu Cys Tyr Lys
    210                 215                 220

Trp Ser His Ile Gly Glu Thr Ser Ser His Leu Arg Ser Lys Val Tyr
225                 230                 235                 240

Ala Ala Phe Gly Gly Ser Ser Pro Cys Leu Lys Gly Leu Met Ser Leu
                245                 250                 255

Trp Ala Ser Trp Leu Pro Arg Gly Arg Pro
            260                 265
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<210> 535
<211> 6082
<212> DNA
<213> Homo sapiens

<400> 535
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cggagcccgc ggccactgcc gcctgatcag cgcgaccccg gcccgcgccc gccccgcccg 180
gcaagatgct gcccgtgtac caggaggtga agcccaaccc gctgcaggac gcgaacctct 240
gctcacgcgt gttcttctgg tggctcaatc ccttgtttaa aattggccat aaacggagat 300
tagaggaaga tgatatgtat tcagtgctgc cagaagaccg ctcacagcac cttggagagg 360
agttgcaagg gttctgggat aaagaagttt taagagctga gaatgacgca cagaagcctt 420
ctttaacaag agcaatcata aagtgttact ggaaatctta tttagttttg ggaattttta 480
cgttaattga ggaaagtgcc aaagtaatcc agcccatatt tttgggaaaa attattaatt 540
attttgaaaa ttatgatccc atggattctg tggctttgaa cacagcgtac gcctatgcca 600
cggtgctgac tttttgcacg ctcattttgg ctatactgca tcacttatat ttttatcacg 660
ttcagtgtgc tgggatgagg ttacgagtag ccatgtgcca tatgatttat cggaaggcac 720
ttcgtcttag taacatggcc atggggaaga caaccacagg ccagatagtc aatctgctgt 780
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Glu Asn Arg Ser Glu Gly Lys Val Gly Phe Gln Ala Tyr Lys Asn Tyr
690 695 700

Phe Arg Ala Gly Ala His Trp Ile Val Phe Ile Phe Leu Ile Leu Leu
705 710 715 720

Asn Thr Ala Ala Gln Val Ala Tyr Val Leu Gln Asp Trp Trp Leu Ser
725 730 735

Tyr Trp Ala Asn Lys Gln Ser Met Leu Asn Val Thr Val Asn Gly Gly
740 745 750

Gly Asn Val Thr Glu Lys Leu Asp Leu Asn Trp Tyr Leu Gly Ile Tyr
755 760 765

Ser Gly Leu Thr Val Ala Thr Val Leu Phe Gly Ile Ala Arg Ser Leu
770 775 780

Leu Val Phe Tyr Val Leu Val Asn Ser Ser Gln Thr Leu His Asn Lys
785 790 795 800

Met Phe Glu Ser Ile Leu Lys Ala Pro Val Leu Phe Phe Asp Arg Asn
805 810 815

Pro Ile Gly Arg Ile Leu Asn Arg Phe Ser Lys Asp Ile Gly His Leu
820 825 830

Asp Asp Leu Leu Pro Leu Thr Phe Leu Asp Phe Ile Gln Thr Leu Leu
835 840 845

Gln Val Val Gly Val Val Ser Val Ala Val Ala Val Ile Pro Trp Ile
850 855 860

Ala Ile Pro Leu Val Pro Leu Gly Ile Ile Phe Ile Phe Leu Arg Arg
865 870 875 880

Tyr Phe Leu Glu Thr Ser Arg Asp Val Lys Arg Leu Glu Ser Thr Thr
885 890 895

Arg Ser Pro Val Phe Ser His Leu Ser Ser Ser Leu Gln Gly Leu Trp
900 905 910

Thr Ile Arg Ala Tyr Lys Ala Glu Glu Arg Cys Gln Glu Leu Phe Asp
915 920 925

Ala His Gln Asp Leu His Ser Glu Ala Trp Phe Leu Phe Leu Thr Thr
930 935 940

Ser Arg Trp Phe Ala Val Arg Leu Asp Ala Ile Cys Ala Met Phe Val
945 950 955 960

Ile Ile Val Ala Phe Gly Ser Leu Ile Leu Ala Lys Thr Leu Asp Ala
965 970 975

Gly Gln Val Gly Leu Ala Leu Ser Tyr Ala Leu Thr Leu Met Gly Met
980 985 990

Phe Gln Trp Cys Val Arg Gln Ser Ala Glu Val Glu Asn Met Met Ile
995 1000 1005

Ser Val Glu Arg Val Ile Glu Tyr Thr Asp Leu Glu Lys Glu Ala Pro
1010 1015 1020

Trp Glu Tyr Gln Lys Arg Pro Pro Pro Ala Trp Pro His Glu Gly Val
1025 1030 1035 1040

Ile Ile Phe Asp Asn Val Asn Phe Met Tyr Ser Pro Gly Gly Pro Leu
1045 1050 1055

Val Leu Lys His Leu Thr Ala Leu Ile Lys Ser Gln Glu Lys Val Gly
1060 1065 1070

Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser Leu Ile Ser Ala Leu
1075 1080 1085

Phe Arg Leu Ser Glu Pro Glu Gly Lys Ile Trp Ile Asp Lys Ile Leu
1090 1095 1100

Thr Thr Glu Ile Gly Leu His Asp Leu Arg Lys Lys Met Ser Ile Ile
1105 1110 1115 1120

Pro Gln Glu Pro Val Leu Phe Thr Gly Thr Met Arg Lys Asn Leu Asp
1125 1130 1135

Pro Phe Asn Glu His Thr Asp Glu Glu Leu Trp Asn Ala Leu Gln Glu
1140 1145 1150

Val Gln Leu Lys Glu Thr Ile Glu Asp Leu Pro Gly Lys Met Asp Thr
1155 1160 1165

Glu Leu Ala Glu Ser Gly Ser Asn Phe Ser Val Gly Gln Arg Gln Leu
1170 1175 1180

Val Cys Leu Ala Arg Ala Ile Leu Arg Lys Asn Gln Ile Leu Ile Ile
1185 1190 1195 1200

Asp Glu Ala Thr Ala Asn Val Asp Pro Arg Thr Asp Glu Leu Ile Gln
1205 1210 1215

Lys Lys Ser Gly Arg Asn Leu Pro Thr Ala Pro Cys
1220 1225

<210> 538
<211> 1261
<212> PRT
<213> Homo sapiens

<400> 538
Met Tyr Ser Val Leu Pro Glu Asp Arg Ser Gln His Leu Gly Glu Glu

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Leu Gln Gly Phe Trp Asp Lys Glu Val Leu Arg Ala Glu Asn Asp Ala
20 25 30

Gln Lys Pro Ser Leu Thr Arg Ala Ile Ile Lys Cys Tyr Trp Lys Ser
35 40 45

Tyr Leu Val Leu Gly Ile Phe Thr Leu Ile Glu Glu Ser Ala Lys Val
50 55 60

Ile Gln Pro Ile Phe Leu Gly Lys Ile Ile Asn Tyr Phe Glu Asn Tyr
65 70 75 80

Asp Pro Met Asp Ser Val Ala Leu Asn Thr Ala Tyr Ala Tyr Ala Thr
85 90 95

Val Leu Thr Phe Cys Thr Leu Ile Leu Ala Ile Leu His His Leu Tyr
100 105 110

Phe Tyr His Val Gln Cys Ala Gly Met Arg Leu Arg Val Ala Met Cys
115 120 125

His Met Ile Tyr Arg Lys Ala Leu Arg Leu Ser Asn Met Ala Met Gly
130 135 140

Lys Thr Thr Thr Gly Gln Ile Val Asn Leu Leu Ser Asn Asp Val Asn
145 150 155 160

Lys Phe Asp Gln Val Thr Val Phe Leu His Phe Leu Trp Ala Gly Pro
165 170 175

Leu Gln Ala Ile Ala Val Thr Ala Leu Leu Trp Met Glu Ile Gly Ile
180 185 190

Ser Cys Leu Ala Gly Met Ala Val Leu Ile Ile Leu Leu Pro Leu Gln
195 200 205

Ser Cys Phe Gly Lys Leu Phe Ser Ser Leu Arg Ser Lys Thr Ala Thr
210 215 220

Phe Thr Asp Ala Arg Ile Arg Thr Met Asn Glu Val Ile Thr Gly Ile
225 230 235 240

Arg Ile Ile Lys Met Tyr Ala Trp Glu Lys Ser Phe Ser Asn Leu Ile
245 250 255

Thr Asn Leu Arg Lys Lys Glu Ile Ser Lys Ile Leu Arg Ser Ser Cys
260 265 270

Leu Arg Gly Met Asn Leu Ala Ser Phe Phe Ser Ala Ser Lys Ile Ile
275 280 285

Val Phe Val Thr Phe Thr Thr Tyr Val Leu Leu Gly Ser Val Ile Thr
290 295 300

Ala Ser Arg Val Phe Val Ala Val Thr Leu Tyr Gly Ala Val Arg Leu
305 310 315 320

Thr Val Thr Leu Phe Phe Pro Ser Ala Ile Glu Arg Val Ser Glu Ala
325 330 335

Ile Val Ser Ile Arg Arg Ile Gln Thr Phe Leu Leu Leu Asp Glu Ile
340 345 350

Ser Gln Arg Asn Arg Gln Leu Pro Ser Asp Gly Lys Lys Met Val His
355 360 365

Val Gln Asp Phe Thr Ala Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr
370 375 380

Leu Gln Gly Leu Ser Phe Thr Val Arg Pro Gly Glu Leu Leu Ala Val
385 390 395 400

Val Gly Pro Val Gly Ala Gly Lys Ser Ser Leu Leu Ser Ala Val Leu
405 410 415

Gly Glu Leu Ala Pro Ser His Gly Leu Val Ser Val His Gly Arg Ile
420 425 430

Ala Tyr Val Ser Gln Gln Pro Trp Val Phe Ser Gly Thr Leu Arg Ser
435 440 445

Asn Ile Leu Phe Gly Lys Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val
450 455 460

Ile Lys Ala Cys Ala Leu Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly
465 470 475 480

Asp Leu Thr Val Ile Gly Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln
485 490 495

Lys Ala Arg Val Asn Leu Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile
500 505 510

Tyr Leu Leu Asp Asp Pro Leu Ser Ala Val Asp Ala Glu Val Ser Arg
515 520 525

His Leu Phe Glu Leu Cys Ile Cys Gln Ile Leu His Glu Lys Ile Thr
530 535 540

Ile Leu Val Thr His Gln Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile
545 550 555 560

Leu Ile Leu Lys Asp Gly Lys Met Val Gln Lys Gly Thr Tyr Thr Glu
565 570 575

Phe Leu Lys Ser Gly Ile Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn
580 585 590

Glu Glu Ser Glu Gln Pro Pro Val Pro Gly Thr Pro Thr Leu Arg Asn
595 600 605

Arg Thr Phe Ser Glu Ser Ser Val Trp Ser Gln Gln Ser Ser Arg Pro
610 615 620

Ser Leu Lys Asp Gly Ala Leu Glu Ser Gln Asp Thr Glu Asn Val Pro
625 630 635 640

Val Thr Leu Ser Glu Glu Asn Arg Ser Glu Gly Lys Val Gly Phe Gln
645 650 655

Ala Tyr Lys Asn Tyr Phe Arg Ala Gly Ala His Trp Ile Val Phe Ile
660 665 670

Phe Leu Ile Leu Leu Asn Thr Ala Ala Gln Val Ala Tyr Val Leu Gln
675 680 685

Asp Trp Trp Leu Ser Tyr Trp Ala Asn Lys Gln Ser Met Leu Asn Val
690 695 700

Thr Val Asn Gly Gly Gly Asn Val Thr Glu Lys Leu Asp Leu Asn Trp
705 710 715 720

Tyr Leu Gly Ile Tyr Ser Gly Leu Thr Val Ala Thr Val Leu Phe Gly
725 730 735

Ile Ala Arg Ser Leu Leu Val Phe Tyr Val Leu Val Asn Ser Ser Gln
740 745 750

Thr Leu His Asn Lys Met Phe Glu Ser Ile Leu Lys Ala Pro Val Leu
755 760 765

Phe Phe Asp Arg Asn Pro Ile Gly Arg Ile Leu Asn Arg Phe Ser Lys
770 775 780

Asp Ile Gly His Leu Asp Asp Leu Leu Pro Leu Thr Phe Leu Asp Phe
785 790 795 800

Ile Gln Thr Leu Leu Gln Val Val Gly Val Val Ser Val Ala Val Ala
805 810 815

Val Ile Pro Trp Ile Ala Ile Pro Leu Val Pro Leu Gly Ile Ile Phe
820 825 830

Ile Phe Leu Arg Arg Tyr Phe Leu Glu Thr Ser Arg Asp Val Lys Arg
835 840 845

Leu Glu Ser Thr Thr Arg Ser Pro Val Phe Ser His Leu Ser Ser Ser
850 855 860

Leu Gln Gly Leu Trp Thr Ile Arg Ala Tyr Lys Ala Glu Glu Arg Cys
865 870 875 880

Gln Glu Leu Phe Asp Ala His Gln Asp Leu His Ser Glu Ala Trp Phe
885 890 895

Leu Phe Leu Thr Thr Ser Arg Trp Phe Ala Val Arg Leu Asp Ala Ile
900 905 910

Cys Ala Met Phe Val Ile Ile Val Ala Phe Gly Ser Leu Ile Leu Ala
915 920 925

Lys Thr Leu Asp Ala Gly Gln Val Gly Leu Ala Leu Ser Tyr Ala Leu

930 935 940

Thr Leu Met Gly Met Phe Gln Trp Cys Val Arg Gln Ser Ala Glu Val
945 950 955 960

Glu Asn Met Met Ile Ser Val Glu Arg Val Ile Glu Tyr Thr Asp Leu
965 970 975

Glu Lys Glu Ala Pro Trp Glu Tyr Gln Lys Arg Pro Pro Pro Ala Trp
980 985 990

Pro His Glu Gly Val Ile Ile Phe Asp Asn Val Asn Phe Met Tyr Ser
995 1000 1005

Pro Gly Gly Pro Leu Val Leu Lys His Leu Thr Ala Leu Ile Lys Ser
1010 1015 1020

Gln Glu Lys Val Gly Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser
1025 1030 1035 1040

Leu Ile Ser Ala Leu Phe Arg Leu Ser Glu Pro Glu Gly Lys Ile Trp
1045 1050 1055

Ile Asp Lys Ile Leu Thr Thr Glu Ile Gly Leu His Asp Leu Arg Lys
1060 1065 1070

Lys Met Ser Ile Ile Pro Gln Glu Pro Val Leu Phe Thr Gly Thr Met
1075 1080 1085

Arg Lys Asn Leu Asp Pro Phe Asn Glu His Thr Asp Glu Glu Leu Trp
1090 1095 1100

Asn Ala Leu Gln Glu Val Gln Leu Lys Glu Thr Ile Glu Asp Leu Pro
1105 1110 1115 1120

Gly Lys Met Asp Thr Glu Leu Ala Glu Ser Gly Ser Asn Phe Ser Val
1125 1130 1135

Gly Gln Arg Gln Leu Val Cys Leu Ala Arg Ala Ile Leu Arg Lys Asn
1140 1145 1150

Gln Ile Leu Ile Ile Asp Glu Ala Thr Ala Asn Val Asp Pro Arg Thr
1155 1160 1165

Asp Glu Leu Ile Gln Lys Lys Ile Arg Glu Lys Phe Ala His Cys Thr
1170 1175 1180

Val Leu Thr Ile Ala His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys
1185 1190 1195 1200

Ile Met Val Leu Asp Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr
1205 1210 1215

Val Leu Leu Gln Asn Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln
1220 1225 1230

Leu Gly Lys Ala Glu Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln Arg
1235 1240 1245

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Trp Gly Phe Thr Met Leu Ala Arg Leu Val Ser Asn Ser
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<210> 539
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

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Cys Leu Ser His Ser Val Ala Val Val Thr
 1               5                  10

<210> 540
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 540
Ala Val Val Thr Ala Ser Ala Ala Leu
 1               5

<210> 541
<211> 14
<212> PRT
<213> Homo sapiens

<400> 541
Leu Ala Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu
                 5                  10

<210> 542
<211> 15
<212> PRT
<213> Homo sapiens

<400> 542
Thr Gln Val Val Phe Asp Lys Ser Asp Leu Ala Lys Tyr Ser Ala
                 5                  10                  15

<210> 543
<211> 12
<212> PRT
<213> Homo sapiens

<400> 543
Phe Met Gly Ser Ile Val Gln Leu Ser Gln Ser Val
                 5                  10
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<210> 544
<211> 18
<212> PRT
<213> Homo sapiens

<400> 544
Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val Glu Glu Lys Phe
5 10 15

Met Thr

<210> 545
<211> 18
<212> PRT
<213> Homo sapiens

<400> 545
Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg Ala Val Tyr Leu Ala
5 10 15

Ser Val

<210> 546
<211> 29
<212> PRT
<213> Homo sapiens

<400> 546
Phe Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly
5 10 15

Thr Glu Ala Arg Arg His Tyr Asp Glu Gly Val Arg Met
20 25

<210> 547
<211> 58
<212> PRT
<213> Homo sapiens

<400> 547
Val Ala Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu
5 10 15

Ser Ala Pro Ser Leu Ser Pro His Cys Cys Pro Cys Arg Ala Arg Leu
20 25 30

Ala Phe Arg Asn Leu Gly Ala Leu Leu Pro Arg Leu His Gln Leu Cys
35 40 45

Cys Arg Met Pro Arg Thr Leu Arg Arg Leu
50 55

<210> 548
<211> 18
<212> PRT
<213> Homo sapiens

<400> 548
Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu Gly Thr Gln Glu
5 10 15

Glu Cys

<210> 549
<211> 18
<212> PRT
<213> Homo sapiens

<400> 549
Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg
5 10 15

Gln Ala

<210> 550
<211> 14
<212> PRT
<213> Homo sapiens

<400> 550
Ser Asp His Trp Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe
5 10

<210> 551
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 551
Phe Asp Lys Ser Asp Leu Ala Lys Tyr Ser Ala
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<210> 552
<211> 2577
<212> DNA
<213> Homo sapiens

<400> 552
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tcataccagt ccacggacta ttatgaacca caccacacag gaggaggtga gcactaggca 180
agccaaggaa gcttcacctg tacttacagc cacacgccat ggctcatatt acagcctgaa 240

ctctgcctcc actcagatca gtgataacat tagaaactca ttggagcacg aaccctgttg 300
tgaactgcct atccgaagga tctaggttgt gtgcttcgta tgagaatcta atgccagatg 360
atctatcatt gtctcacttt gcccccagat aagaccatct agttgcagaa aaataagctc 420
agagcttcca ctgattctac attatggata tgtgccgccg aagcaagcac aaagccctac 480
ttttacacat gcctagtgat gcttcatgga caaggcttgg ctctgttgag tccaactaac 540
ctacctgaga ttctgagatt tctcttcaat ggcttcctgt gagctagagt ttgaaaatat 600
cttaaaatct tgagctagag atggaagtag cttggacgat tttcattatc atgtaaatcg 660
ggtcactcaa ggggccaacc acagctggga gccactgctc aggggaaggt tcatatggga 720
ctttctactg cccaaggttc tatacaggat ataaaggtgc ctcacagtat agatctggta 780
gcaaagaaga agaaacaaac actgatctct ttctgccacc cctctgaccc tttggaactc 840
ctctgaccct ttagaacaag cctacctaat atctgctaga gaaaagacca acaacggcct 900
caaaggatct cttaccatga aggtctcagc taattcttgg ctaagatgtg ggttccacat 960
taggttctga atatgggggg aagggtcaat ttgctcattt tgtgtgtgga taaagtcagg 1020
atgcccaggg gccagagcag ggggctgctg ctttgggaac aatggctgag catataacca 1080
taggtatggg aacaaaaaac atcaaagtca ctgtatcaat tgccatgaag actcgaggga 1140
cctgaatcta ccgattcatc ttaaggcagc aggaccagtt tgagtggcaa caatgcagca 1200
gcagaatcaa tggaaacaac agaatgattg caatgtcctt tttttctcc tccttctgac 1260
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aggagtatct aggacatagt ccccagaaga cagtacaaga ctttctgata aactggacat 1380
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aaagtcctga gataaagaat cctgcaccca ctggtacttc taacttgtct tgttttttgt 1560
ctgwtttctg gctgatgcag gggactaact cactgccacg cgaaaactac ctgaactgaa 1620
ctatgacatc tcacctgata tgtaagatgt aactgttata attattttaa acctcaattt 1680
agcattaact agcctttttaa tgtaaacact tacacattat gaygactaga aacagcatac 1740
tctctggccg tctgtccaga tagatcttga gaagatacat caatgttttg ctcaagtaga 1800
aggctgacta tacttgccga tccacaacat acagcaagta tgagagcagt tctaaaatga 1860
cagagatagg aacagtaata aagttattkt aaaagctaat ttgatatact ttaccaattt 1920
aacatcttgc ctgtccgtgc agaatcaaac atttacatgc actaaaagac ataagcatct 1980
tcagtgctca agtgttcatc tttgtaaaat accaccaagg ttaaaaggaa gggacaaaaa 2040
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ataaataaga gctctctgca tgctgaaagc aagtaagatt aataataatg gtaagaatag 2280
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agttaggaat taaacccagt attgtgtgaa tctaaagcct aactttttc tctttatcac 2520
ccacctacgg cttgtcttca ttaaaggaaa agtgtatcca cttaaaaaaa aaaaaaa 2577

<210> 553
<211> 58
<212> PRT
<213> Homo sapiens

<400> 553
Ser Ile Cys Asn Met Thr Cys Ala Ser Val Phe Phe Cys Asp Gln Lys
5 10 15

Phe Leu Thr Phe Ser Phe Leu Ser Met Val Glu Pro Pro Arg Ala Gly
20 25 30

Val Leu Asn Ser Gln Ala Thr Asp Ser Tyr Gln Ser Thr Asp Tyr Tyr
35 40 45

Glu Pro His His Thr Gly Gly Gly Glu His
50 55

<210> 554
<211> 59
<212> PRT
<213> Homo sapiens

<400> 554
Leu Gln Lys Asn Lys Leu Arg Ala Ser Thr Asp Ser Thr Leu Trp Ile
5 10 15

Cys Ala Ala Glu Ala Ser Thr Lys Pro Tyr Phe Tyr Thr Cys Leu Val
20 25 30

Met Leu His Gly Gln Gly Leu Ala Leu Leu Ser Pro Thr Asn Leu Pro
35 40 45

Glu Ile Leu Arg Phe Leu Phe Asn Gly Phe Leu
50 55

<210> 555
<211> 71
<212> PRT
<213> Homo sapiens

<400> 555
Leu Gly Arg Phe Ser Leu Ser Cys Lys Ser Gly His Ser Arg Gly Gln
5 10 15

Pro Gln Leu Gly Ala Thr Ala Gln Gly Lys Val His Met Gly Leu Ser
20 25 30

Thr Ala Gln Gly Ser Ile Gln Asp Ile Lys Val Pro His Ser Ile Asp
35 40 45

Leu Val Ala Lys Lys Lys Lys Gln Thr Leu Ile Ser Phe Cys His Pro
50 55 60

Ser Asp Pro Leu Glu Leu Leu
65 70

<210> 556
<211> 81
<212> PRT
<213> Homo sapiens

<400> 556
Asn His Pro Glu Gln Gly Ser Ser Thr Pro Arg Pro Gln Thr His Thr
5 10 15

Ser Pro Arg Thr Ile Met Asn His Thr Thr Gln Glu Glu Val Ser Thr
20 25 30

Arg Gln Ala Lys Glu Ala Ser Pro Val Leu Thr Ala Thr Arg His Gly
35 40 45

Ser Tyr Tyr Ser Leu Asn Ser Ala Ser Thr Gln Ile Ser Asp Asn Ile

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     50                  55                  60

Arg Asn Ser Leu Glu His Glu Pro Cys Cys Glu Leu Pro Ile Arg Arg
 65                 70                  75                  80

Ile
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<210> 557
<211> 54
<212> PRT
<213> Homo sapiens

<400> 557

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Ser Leu Ser Ala Thr Pro Leu Thr Leu Trp Asn Ser Ser Asp Pro Leu
                  5                  10                  15

Glu Gln Ala Tyr Leu Ile Ser Ala Arg Glu Lys Thr Asn Asn Gly Leu
             20                  25                  30

Lys Gly Ser Leu Thr Met Lys Val Ser Ala Asn Ser Trp Leu Arg Cys
         35                  40                  45

Gly Phe His Ile Arg Phe
     50
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<210> 558
<211> 77
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> (1)...(77)
<223> Xaa = Any amino acid

<400> 558

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Asn Asp Arg Asp Arg Asn Ser Asn Lys Val Ile Xaa Lys Ala Asn Leu
                  5                  10                  15

Ile Tyr Phe Thr Asn Leu Thr Ser Cys Leu Ser Val Gln Asn Gln Thr
             20                  25                  30

Phe Thr Cys Thr Lys Arg His Lys His Leu Gln Cys Ser Ser Val His
         35                  40                  45

Leu Cys Lys Ile Pro Pro Arg Leu Lys Gly Arg Asp Lys Lys Lys Lys
     50                  55                  60

Pro Ser Tyr Leu Ser Gly Val Leu His Ser Arg Ser Tyr
 65                 70                  75
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<210> 559
<211> 50
<212> PRT

<213> Homo sapiens

<400> 559
Thr Leu Pro Pro Leu Arg Ser Val Ile Thr Leu Glu Thr His Trp Ser
                5   10   15

Thr Asn Pro Val Val Asn Cys Leu Ser Glu Gly Ser Arg Leu Cys Ala
            20   25   30

Ser Tyr Glu Asn Leu Met Pro Asp Asp Leu Ser Leu Ser His Phe Ala
        35   40   45

Pro Arg
    50

<210> 560
<211> 56
<212> PRT
<213> Homo sapiens

<400> 560
Ile Gly Ser Leu Lys Gly Pro Thr Thr Ala Gly Ser His Cys Ser Gly
                5   10   15

Glu Gly Ser Tyr Gly Thr Phe Tyr Cys Pro Arg Phe Tyr Thr Gly Tyr
            20   25   30

Lys Gly Ala Ser Gln Tyr Arg Ser Gly Ser Lys Glu Glu Glu Thr Asn
        35   40   45

Thr Asp Leu Phe Leu Pro Pro Leu
    50   55

<210> 561
<211> 57
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> (1)...(57)
<223> Xaa = Any amino acid

<400> 561
Val Leu His Leu Asp Gln Met Asn Asn Val Gly Ile Xaa Met Asp Lys
                5   10   15

Gly Leu Lys Ser Pro Glu Ile Lys Asn Pro Ala Pro Thr Gly Thr Ser
            20   25   30

Asn Leu Ser Cys Phe Leu Ser Xaa Phe Trp Leu Met Gln Gly Thr Asn
        35   40   45

Ser Leu Pro Arg Glu Asn Tyr Leu Asn
    50   55

<210> 562
<211> 59
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> (1)...(59)
<223> Xaa = Any amino acid

<400> 562
Asp Leu Tyr Pro Xaa Arg Ser Gln His Cys Ser Phe Asp Pro Ser Val
5 10 15

Ala Pro Met His Gly Ile Lys Asn Ser Ile Thr Ser Leu Ile Phe Leu
20 25 30

Ile Ser Tyr Leu Xaa Leu Glu Met Ser Ser Leu Ser Glu Ser Leu Val
35 40 45

Leu Ser Ser Gly Asp Tyr Val Leu Asp Thr Pro
50 55

<210> 563
<211> 79
<212> PRT
<213> Homo sapiens

<400> 563
Cys Phe Leu Phe Pro Tyr Leu Trp Leu Tyr Ala Gln Pro Leu Phe Pro
5 10 15

Lys Gln Gln Pro Pro Ala Leu Ala Pro Gly His Pro Asp Phe Ile His
20 25 30

Thr Gln Asn Glu Gln Ile Asp Pro Ser Pro His Ile Gln Asn Leu Met
35 40 45

Trp Asn Pro His Leu Ser Gln Glu Leu Ala Glu Thr Phe Met Val Arg
50 55 60

Asp Pro Leu Arg Pro Leu Leu Val Phe Ser Leu Ala Asp Ile Arg
65 70 75

<210> 564
<211> 64
<212> PRT
<213> Homo sapiens

<400> 564
Ala Cys Ser Lys Gly Ser Glu Glu Phe Gln Arg Val Arg Gly Val Ala
5 10 15

Glu Arg Asp Gln Cys Leu Phe Leu Leu Leu Cys Tyr Gln Ile Tyr Thr
20 25 30

Val Arg His Leu Tyr Ile Leu Tyr Arg Thr Leu Gly Ser Arg Lys Ser
35 40 45

His Met Asn Leu Pro Leu Ser Ser Gly Ser Gln Leu Trp Leu Ala Pro
50 55 60

<210> 565
<211> 57
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> (1)...(57)
<223> Xaa = Any amino acid

<400> 565
Leu Tyr Tyr Cys Ser Tyr Leu Cys His Phe Arg Thr Ala Leu Ile Leu
5 10 15

Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln
20 25 30

Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu
35 40 45

Tyr Ala Val Ser Ser Xaa His Asn Val
50 55

<210> 566
<211> 55
<212> PRT
<213> Homo sapiens

<400> 566
Ile Leu Leu Glu Phe Phe Arg Asn Gln Arg Gly Ser Leu Asn Pro Arg
5 10 15

Lys Thr Val Pro Phe Ile Lys Ser Glu Gly Gly Glu Lys Lys Gly His
20 25 30

Cys Asn His Ser Val Val Ser Ile Asp Ser Ala Ala Ala Leu Leu Pro
35 40 45

Leu Lys Leu Val Leu Leu Pro
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<210> 567
<211> 51
<212> PRT
<213> Homo sapiens

<400> 567
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Leu Thr Leu Ser Thr His Lys Met Ser Lys Leu Thr Leu Pro Pro Ile
        35   40   45

Phe Arg Thr
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<210> 568
<211> 75
<212> PRT
<213> Homo sapiens

<400> 568
Lys Val Gly Glu Tyr Ile Leu Gln Ser Leu Leu Arg Ile Arg Lys Ile
                5   10   15

Tyr Val Ala Phe Asn Ser Val Pro Ser Thr Cys Leu Leu Ala Ser Leu
            20   25   30

Thr Glu Thr Pro Val Thr Thr Ile Leu Thr Ile Ile Ile Asn Leu Thr
        35   40   45

Cys Phe Gln His Ala Glu Ser Ser Tyr Leu Phe Tyr Pro Leu Ala Asp
    50   55   60

Phe Leu Leu Gln His Ile Ser Leu Gly Lys Leu
65   70   75

<210> 569
<211> 4809
<212> DNA
<213> Homo sapiens

<400> 569
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<210> 570
<211> 951
<212> DNA
<213> Homo sapiens

<400> 570
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<210> 571
<211> 819
<212> DNA
<213> Homo sapiens

<400> 571
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<210> 572
<211> 203
<212> DNA
<213> Homo sapiens

<400> 572
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<210> 573
<211> 132
<212> PRT
<213> Homo sapiens

<400> 573
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Met Val Glu Gly Glu Gly Glu Ala Arg His Val Leu His Gly Gly Arg
                5                   10                  15

Arg Glu Arg Val Arg Gly Glu Thr Ala Thr Asn Phe Phe Phe Leu Arg
            20                  25                  30

Gln Glu Ser Gly Pro Val Ala Gln Ala Gly Val Gln Trp His Asp Leu
        35                  40                  45

Ser Ser Leu Gln Pro Leu Pro His Arg Phe Lys Gln Phe Ser Cys Leu
    50                  55                  60

Ser Leu Pro His Ser Trp Asp His Arg Tyr Ala Pro Pro His Leu Ala
65                  70                  75                  80

Asn Phe Cys Ser Phe Ser Arg Asp Gly Val Ser Leu Cys Cys Ser Gly
                85                  90                  95

Trp Ser Lys Thr Pro Gly Leu Gln Gln Ser Ala Cys Leu Gly Leu Pro
            100                 105                 110

Lys Cys Trp Gly Tyr Arg His Lys Pro Pro His Pro Ala Cys His Ile
        115                 120                 125

Leu Leu Asn Tyr
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<210> 574
<211> 62
<212> PRT
<213> Homo sapiens

<400> 574
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Met Thr His Ser Ser Ala Trp Leu Glu Arg Pro Gln Glu Thr Tyr Asn
                5                   10                  15

His Gly Gly Arg Arg Arg Gly Ser Lys Ala Arg Leu Thr Trp Trp Gln
            20                  25                  30

Glu Arg Thr Ser Glu Gly Gly Asp Cys His Lys Leu Phe Phe Phe Glu
        35                  40                  45

Thr Arg Val Trp Pro Cys Cys Pro Gly Trp Ser Ala Val Ala
    50                  55                  60
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<210> 575

<211> 76
<212> PRT
<213> Homo sapiens

<400> 575
Met Val Lys Ser Arg Phe Thr Lys Asn Thr Lys Ile Thr Gln Ala Trp
5 10 15

Trp Arg Ala Pro Val Ile Pro Gly Thr Arg Glu Ala Glu Gly Gly Glu
20 25 30

Ser Leu Glu Pro Gly Arg Leu Arg Glu Glu Asn Arg Leu Asn Pro Gly
35 40 45

Gly Arg Gly Cys Ser Glu Pro Arg Ser Cys Cys Cys Thr Pro Ala Trp
50 55 60

Ser Thr Glu Gln Asp Ser Ala Ser Lys Thr Asn Lys
65 70 75

<210> 576
<211> 68
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> (1)...(68)
<223> Xaa = Any Amino Acid

<400> 576
Met Leu Gly Lys Ser Arg Ala Val Cys Leu Pro Ser Thr Thr Val Thr
5 10 15

Thr Val Cys Tyr Leu Ala Ser Ser Ser Ala Ser Arg Glu Thr Ala Thr
20 25 30

Arg Gln Ala Pro Gly Asn Trp Lys Met Xaa Ser Lys Cys His Ala Gln
35 40 45

Leu Leu Phe Thr Phe Tyr Leu Asn His Phe Tyr Gln Ile Arg Leu Asn
50 55 60

Pro Gly Tyr Ser
65

<210> 577
<211> 57
<212> PRT
<213> Homo sapiens

<400> 577
Met Tyr Leu Glu Asn Ser Phe Tyr Cys Gln Met Ile Leu Leu Lys Arg
5 10 15

Cys Arg Leu Ser Lys Ile Ser Thr Gln Arg Val Val Pro Asp Gly Pro

20 25 30

Pro Ala Pro Val Pro Gly Ser Phe Pro Met Phe Pro Arg Phe Gly Phe
35 40 45

Arg Leu Ala Pro Pro Ala Asp Thr Pro
50 55

<210> 578
<211> 51
<212> PRT
<213> Homo sapiens

<400> 578
Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu Leu Tyr Ile Arg His
5 10 15

His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr Lys Lys Leu Asn Tyr
20 25 30

Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His Ile Ala Lys Val Tyr
35 40 45

Gln Pro His
50

<210> 579
<211> 56
<212> PRT
<213> Homo sapiens

<400> 579
Met His Phe Thr Phe Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu
5 10 15

Leu Tyr Ile Arg His His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr
20 25 30

Lys Lys Leu Asn Tyr Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His
35 40 45

Ile Ala Lys Val Tyr Gln Pro His
50 55

<210> 580
<211> 67
<212> PRT
<213> Homo sapiens

<400> 580
Met Glu Leu Arg Thr Lys Ala Leu Arg Thr Ala Gln Gln Leu Thr Ser
5 10 15

Cys Val Thr Ala Leu Lys Ala Ala Gly Pro Pro Leu Thr Phe Trp Lys
20 25 30

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Gly Lys Trp Val Gln Cys Cys Leu Pro Leu Trp Gly Leu Leu Gly Ser
         35                  40                  45

His Ala Phe Tyr Ile Tyr Ala Val Asp Ile Phe Met Phe Pro Gly Ser
     50                  55                  60

Phe Ile His
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<210> 581
<211> 77
<212> PRT
<213> Homo sapiens

<400> 581
Met Leu Glu Val Lys Phe Glu Val Ser Leu Arg Pro Thr Gly Asn Glu
                  5                  10                  15

Thr Ala Gly Gln Thr His Gly Thr Gln Asp Lys Gly Ser Lys Asp Ser
             20                  25                  30

Thr Ala Ala Asp Ile Leu Cys Asp Ser Leu Glu Ser Ser Arg Pro Ala
         35                  40                  45

Ala His Ile Leu Glu Gly Lys Met Gly Thr Met Leu Ser Ala Thr Leu
     50                  55                  60

Gly Pro Ser Trp Val Thr Cys Ile Leu His Leu Cys Ser
 65                  70                  75


<210> 582
<211> 51
<212> PRT
<213> Homo sapiens

<400> 582
Met Leu Phe Leu Gln Thr Ile Asp Thr Lys Cys Thr Gly Ile Glu Ile
                  5                  10                  15

Asn Arg Asn Trp Ser Lys Val Trp His Thr His Ser His Val Asp Val
             20                  25                  30

Lys Leu Cys Leu Glu Phe Leu Cys Gly Val Trp Phe Gly Leu Gly Phe
         35                  40                  45

Leu Gly Val
     50


<210> 583
<211> 60
<212> PRT
<213> Homo sapiens

<400> 583
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Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg
5 10 15

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro
20 25 30

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly
35 40 45

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys
50 55 60

<210> 584
<211> 76
<212> PRT
<213> Homo sapiens

<400> 584
Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys
5 10 15

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg
20 25 30

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro
35 40 45

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly
50 55 60

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys
65 70 75

<210> 585
<211> 50
<212> PRT
<213> Homo sapiens

<400> 585
Met Val Tyr Arg Phe Gly Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu
5 10 15

Ala Ser Leu Gly Ser Ser Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp
20 25 30

Arg Gln Ala Asp Pro Ser Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu
35 40 45

Leu Phe
50

<210> 586
<211> 60
<212> PRT
<213> Homo sapiens

<400> 586
Met Leu Val His Ile Tyr Ser Cys Cys Gly Met Val Tyr Arg Phe Gly
5 10 15

Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu Ala Ser Leu Gly Ser Ser
20 25 30

Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp Arg Gln Ala Asp Pro Ser
35 40 45

Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe
50 55 60

<210> 587
<211> 1408
<212> DNA
<213> Homo sapiens

<400> 587
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aaaaaaaaaa aaaaaaaaaa rwmgaccc 1408

<210> 588
<211> 81
<212> PRT
<213> Homo sapiens

<400> 588
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5 10 15

Leu Gln Phe Arg Gln Tyr Asn Lys Ser Val His Glu Val Asn Leu Lys
20 25 30

Gly Ala Cys Phe Thr Val Ala Gly Leu Pro Arg Ala Trp Thr Thr Gln
35 40 45

Tyr Ser Ile Ile Asp Lys Arg Ile Arg Gln Glu Ile Tyr Thr Cys Cys
50 55 60

Leu Ala Phe Val Val Ile Tyr Thr Asn Glu Asn Met Tyr Tyr Ser Tyr
65 70 75 80

Ile

<210> 589
<211> 157
<212> PRT
<213> Homo sapiens

<400> 589
Met Thr Met Cys Leu Cys Val Ala Pro Met Gly Arg Ala Thr Arg Met
5 10 15

Ser Val Thr Cys Asp Arg Leu His Ala Asn Ser Arg Val Arg Tyr Leu
20 25 30

Trp Cys Gln Lys Asp His Val Pro Gln Met Gln Asp Gln Asp Leu Glu
35 40 45

Met Glu Ser Met Lys Ala Leu Glu Lys Leu Val Lys Arg Arg His Pro
50 55 60

Pro Val Ile Phe Ala Ser Leu Val Gln Asn Val Thr Lys Met Pro Arg
65 70 75 80

Met Ser Gly Val Cys Val Ile Leu Thr Val Leu Lys Pro Thr Ser Ile
85 90 95

Pro Ser Ala Leu Leu Met Gly Asn Leu Met Ile Met His Ala Lys Ser
100 105 110

Lys Lys His Arg Val Arg Asn Arg Arg Lys Leu Lys Ser Cys Leu Trp
115 120 125

Val Asp Val Lys Ile Thr Gln Leu Gln Leu Leu Ser Leu Lys Met Gly
130 135 140

Ile Met Gln Glu Gln Ile Met Gln Arg Met Leu Thr Asn
145 150 155

<210> 590
<211> 347
<212> PRT
<213> Homo sapiens

<400> 590
Met Leu Leu Ile Val Ala Arg Pro Val Lys Leu Ala Ala Phe Pro Thr
5 10 15

```
Ser Leu Ser Asp Cys Gln Thr Pro Thr Gly Trp Asn Cys Ser Gly Tyr
            20                  25                  30

Asp Asp Arg Glu Asn Asp Leu Phe Leu Cys Asp Thr Asn Thr Cys Lys
        35                  40                  45

Phe Asp Gly Glu Cys Leu Arg Ile Gly Asp Thr Val Thr Cys Val Cys
    50                  55                  60

Gln Phe Lys Cys Asn Asn Asp Tyr Val Pro Val Cys Gly Ser Asn Gly
65                  70                  75                  80

Glu Ser Tyr Gln Asn Glu Cys Tyr Leu Arg Gln Ala Ala Cys Lys Gln
                85                  90                  95

Gln Ser Glu Ile Leu Val Val Ser Glu Gly Ser Cys Ala Thr Asp Ala
            100                 105                 110

Gly Ser Gly Ser Gly Asp Gly Val His Glu Gly Ser Gly Glu Thr Ser
        115                 120                 125

Gln Lys Glu Thr Ser Thr Cys Asp Ile Cys Gln Phe Gly Ala Glu Cys
    130                 135                 140

Asp Glu Asp Ala Glu Asp Val Trp Cys Val Cys Asn Ile Asp Cys Ser
145                 150                 155                 160

Gln Thr Asn Phe Asn Pro Leu Cys Ala Ser Asp Gly Lys Ser Tyr Asp
                165                 170                 175

Asn Ala Cys Gln Ile Lys Glu Ala Ser Cys Gln Lys Gln Glu Lys Ile
            180                 185                 190

Glu Val Met Ser Leu Gly Arg Cys Gln Asp Asn Thr Thr Thr Thr Thr
        195                 200                 205

Lys Ser Glu Asp Gly His Tyr Ala Arg Thr Asp Tyr Ala Glu Asn Ala
    210                 215                 220

Asn Lys Leu Glu Glu Ser Ala Arg Glu His His Ile Pro Cys Pro Glu
225                 230                 235                 240

His Tyr Asn Gly Phe Cys Met His Gly Lys Cys Glu His Ser Ile Asn
                245                 250                 255

Met Gln Glu Pro Ser Cys Arg Cys Asp Ala Gly Tyr Thr Gly Gln His
            260                 265                 270

Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr Val Val Pro Gly Pro Val
        275                 280                 285

Arg Phe Gln Tyr Val Leu Ile Ala Ala Val Ile Gly Thr Ile Gln Ile
    290                 295                 300

Ala Val Ile Cys Val Val Val Leu Cys Ile Thr Arg Lys Cys Pro Arg
305                 310                 315                 320
```

```
Ser Asn Arg Ile His Arg Gln Lys Gln Asn Thr Gly His Tyr Ser Ser
                325                 330                 335

Asp Asn Thr Thr Arg Ala Ser Thr Arg Leu Ile
            340                 345


<210> 591
<211> 565
<212> DNA
<213> Homo sapien

<400> 591
actaaagcaa atgaacaagc tgacttgcta gtatcatctg cattcattga agcacaagaa      60
cttcatgcct tgactcatgt aaatgcaata ggattaaaaa ataaatttga tatcacatgg     120
aaacagacaa aaaatattgt acaacattgc acccagtgtc agattctaca cctggccact     180
caggaagcaa gagttaatcc cagaggtcta tgtcctaatg tgttatggca aatggatgtc     240
atgcacgtac cttcatttgg aaaattgtca tttgtccatg tgacagttga tacttattca     300
catttcatat gggcaacctg ccagacagga gaaagtactt cccatgttaa aagacattta     360
ttatcttgtt ttcctgtcat gggagttcca gaaaaagtta aaacagacaa tgggccaggt     420
tactgtagta aagcatttca aaaattctta aatcagtgga aaattacaca tacaatagga     480
attctctata attcccaagg acaggccata attgaaggaa ctaatagaac actcaaagct     540
caattggtta aacaaaaaaa aaaaa                                           565


<210> 592
<211> 188
<212> PRT
<213> Homo sapien

<400> 592
Thr Lys Ala Asn Glu Gln Ala Asp Leu Leu Val Ser Ser Ala Phe Ile
 1               5                  10                  15
Glu Ala Gln Glu Leu His Ala Leu Thr His Val Asn Ala Ile Gly Leu
            20                  25                  30
Lys Asn Lys Phe Asp Ile Thr Trp Lys Gln Thr Lys Asn Ile Val Gln
        35                  40                  45
His Cys Thr Gln Cys Gln Ile Leu His Leu Ala Thr Gln Glu Ala Arg
    50                  55                  60
Val Asn Pro Arg Gly Leu Cys Pro Asn Val Leu Trp Gln Met Asp Val
65                  70                  75                  80
Met His Val Pro Ser Phe Gly Lys Leu Ser Phe Val His Val Thr Val
                85                  90                  95
Asp Thr Tyr Ser His Phe Ile Trp Ala Thr Cys Gln Thr Gly Glu Ser
            100                 105                 110
Thr Ser His Val Lys Arg His Leu Leu Ser Cys Phe Pro Val Met Gly
        115                 120                 125
Val Pro Glu Lys Val Lys Thr Asp Asn Gly Pro Gly Tyr Cys Ser Lys
    130                 135                 140
Ala Phe Gln Lys Phe Leu Asn Gln Trp Lys Ile Thr His Thr Ile Gly
145                 150                 155                 160
Ile Leu Tyr Asn Ser Gln Gly Gln Ala Ile Ile Glu Gly Thr Asn Arg
                165                 170                 175
Thr Leu Lys Ala Gln Leu Val Lys Gln Lys Lys Lys
            180                 185

<210> 593
<211> 271
```

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(271)
<223> n = A,T,C or G

<400> 593
```
actttatgtt cnagtgcana aanccncctg gattgccacc ntactctcag ggctgtgant      60
tgtgcnccca nagcaacctg ggcacgcggg gacaggggggg ccnacaattg agggagcggt    120
gtccctagct ggggtctata catgncnggg naagggcngc tgagtnccat nagcaaagga     180
nctagnatnt gcgggggtgc ggcctgggcc taccctttna agcatccntn gatccactcc    240
angaanccng gggtagncag gtttnccaac a                                    271
```

<210> 594
<211> 376
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(376)
<223> n = A,T,C or G

<400> 594
```
cctttggggg ngggggggaac ctttaccatt gtncccccttt atttcatttg gttngggttc    60
gcgccctcnn gggccaacaa agttatcgtn nttgaagaga anattttttt ggnttngncc     120
cgattaagcg ncaaatgtgt agcaaaangc cgtgccactt gtggcgtagc tncgtcgggt     180
cgattcgacg acaaggcgtn gcgcgntanc gttagtctcn aatngacccn gtggcatgag     240
cccacgangg nttcgtgtcg tcacatggnc tctagacata acgcncnccn ttttttncag     300
agggggntgc cgcccttagg gaggnagggg tggggacact agccaancca nantctnacc     360
ccattgaaga aaaggn                                                     376
```

<210> 595
<211> 242
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(242)
<223> n = A,T,C or G

<400> 595
```
agnctgctgn tcgtnccctn tatgtggctt catnntgagg acaanagtng cactgaggct     60
tgngnatgcc aggcaaggnc aagctggctc aaaaagcatc cacccacctc tgnaangggt    120
atgccangag cangtgcacc agtcccaact angagncccn ggcatgntac atcttcttcc    180
acccctnaaa ntttgngcta caangnccat ttttcttttt ctcttaaggg ncncntggct    240
tc                                                                    242
```

<210> 596
<211> 535
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(535)
<223> n = A,T,C or G

<400> 596
accagttgga tactgctaaa nagatattta tgcagcctca tatgttaagt cgtatatttt 60
gaaagctttt taaatttttt ctttaagaag attttagatg cttatcactg agtaccagag 120
ggatgtaggc tgatgccctt atcaacaaag tcagggactg tggcacacaa ggattgacta 180
ctgcagacac ggccacaatg ctacctctag agggcctgaa tccccctgcc ctctctggtg 240
gggagaaggg ctggcagagc cattagcatg ggctccggcc aatcctggcc actttgacac 300
tcctggtgct gacccagggt cctggaggaa gggatgaggt gggcagtaga gatgctcagg 360
gcagtggccc ctttccatcc acactggaac tatttcagta ttttaccacc aattcagcca 420
ttcccttgtg cgctggctga acatcagccc tgctccaggt ctcagtttcc cctttgtaaa 480
gggaaagctc tggattcagg gagtgatgaa gaggtcatca tggtcttgag aattc 535

<210> 597
<211> 257
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(257)
<223> n = A,T,C or G

<400> 597
tttcnatacc caaaantacc ccatattang accanacatt tgtctnggaa aaattaccat 60
tntntaacnt ttgggccacc tgagannaaa tgggtgtaat ncatgataag atggancagn 120
attnctctta agatnngatn agaccccgtt tttcacggaa catatccaag nacccaatag 180
gnaacaagcc acgggnggag tcacaaacat atattcttta ctctcataat ccgtnncaca 240
naactnttgn acttgac 257

<210> 598
<211> 222
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(222)
<223> n = A,T,C or G

<400> 598
nntggntacc gtcnaaactt nncttggtac ccgagctcgg atccactagt ccagtgtggt 60
ggaattccat tgtgttgggc tataagctgt aatagtggag ncgtgctngg ttcattgcan 120
nagnccctcc gcanncacnc ttgnnacaac ctgtgagnag gcnataaatt attcacataa 180
tcatcactgc atgaanctga ctcaaacgca tccacntaca cc 222

<210> 599
<211> 238
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(238)
<223> n = A,T,C or G

<400> 599

gcatgacatc ancgatgtnt ttggnnacct ganattngct aaaactngng natgccgggn 60
atgnaggttt ggtantgatc tatgcactca catctcatgg ggacgtttca tgtggagtgn 120
tcgacaangt tgctgnancn gagaagtgat gatctcagtt gaaagggtca tgtgaataca 180
cnttacactt gaaaaagaag cacattggga atatcacgaa acgnccacca acatcctg 238

<210> 600
<211> 232
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(232)
<223> n = A,T,C or G

<400> 600
cgaactattt agactaccta ggaaaattat tttagtatca gaagaatatc aggggtgtag 60
tactcatcag agctaaatga gagcgcttta aaaatgttag tttgtcttcc gccatttcta 120
cagaaagctg caatttcagg ttttcaacct aataggtgat atttaanaaa aaaaaaaagc 180
aatcgcaaat agccccactg cttttacaaa tcatttttc cccaacacaa tg 232

<210> 601
<211> 547
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(547)
<223> n = A,T,C or G

<400> 601
cattgtgttg gggaaaaaat gatttgtata agcagtgggg ctatttgcga ttgctttttt 60
tttttcttaa atatcaccta ttaggttgaa aacctgaaat tgcagctttc tgtagaaatg 120
gcggaagaca aactaacatt tttaaagcgc tctcatttag ctctgatgag tactacaccc 180
ctnatattct tctgatacta aaataatttt cctagtgtag tctaaacttt tttaaaaaga 240
catgtaatcc gcggagttag taactcaaaa cgagtgcatc tnggaagtat cgcagccgtt 300
nctggatnaa attcccagct tgctngcttg ctnagccggg gggcggtnaa aaaaacatct 360
gcagcccngg ggnaaaaacc ttcgcattgt tcttacgtgt ttacgttatt ttatttccct 420
nnagcaaggc ngggganttgg ggactcgaaa tggtacagtt gggctgggga tcgcccttgt 480
tacataaaag ncgtccagaa gagggacggt tacaggcngg ganctccaaa ggtcagtccc 540
tgccatt 547

<210> 602
<211> 826
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(826)
<223> n = A,T,C or G

<400> 602
cggggggnnt tacgtctctc tggacgcttt tattgtacca gggcgatccc agcccaactg 60
taccattcga gtccctactc ctgccttgct ctagggaaat aaaataacgt aaacacgtaa 120
gaacaatgcg aaagcgtttt cttccctagg ctgcagattg tcttcttcac cgcccctgct 180
tagctagcta gctagctggg aatttaatcc agaaacggct tgcgatacct cctagatgca 240

ctcgttttga gttacaaact ccgcggatta catgtctttt taaaaaagtt tagactacac 300
tagggaaaat tattttagta tcagaagaat atcagggggt gtagtactca tcagagctna 360
atgagagcgc tttaaaaatg ttagtttgtc ttccgccatt tctacagaaa gctgcaattt 420
caggttttca ncctaatagg tgatatntaa gaaaaaaaaa acaatcgcan atagcccact 480
gcttttacaa atcatttttc tcttctaggt atagcctgtc aggtggccta atgtattttt 540
gacatctcta ggaattttaa tagaccagaa atgggtgcca gagatatgcc tgcactaatc 600
ttaagtgggg atttatgtat ttctcaanca agtgattaaa gcaaaactag gcacgaatga 660
aatcaagatc tttaggccag aaatcatgaa nanttttana attattttan gaatctgtgg 720
cttctcttct taaaatngaa aaaaaaattg tttaaaccca naaggtctga atacccaagc 780
nccctgaacn anagaacaan gccggagcac cccctcccaa atcccc 826

<210> 603
<211> 817
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(817)
<223> n = A,T,C or G

<400> 603
nnangacttt tgtggtntta tacaattntt ttttctattt ctatgaagag aaagccacag 60
agtcctaaaa taattctaaa actcatcatg actttcttgc ctaaaagatc ttgatttcaa 120
tcgtgcctag ttttgcttta atcacttgct tgagaaatac ataaatcccc acttaagatt 180
agtgcaggca tatctctggc acccatttct ggttctatta aaattcctag agatgtcaaa 240
aattacatta ggccacctga caggctatac ctagaagaga aaaaatgatt tgtaaaagca 300
gtggggctat ttgcgattgc tttttttttt tcttaaatat cacctattag gttgaaaacc 360
tgaaattgca gctttctgta gaaatggcgg aagacaaact aacattttta aagcgctctc 420
atttagctct gatgagtact acacccctga tattcttctg atactaaaat aattttccta 480
gtgtagtcta aactttttta aaaagacatg taatccgcgg agtttgtaac tcaaaacgag 540
tgcatctagg aggtatcgca agccgtttct ggattaaatt cccagctagc ttgcttgctt 600
agcaggggcg ggnaaanaag acatctgcag cctagggaag aaaacctttc gcattgttct 660
tacgtgttta cgttatttta tttcctanaa caaggcngaa ttgggactcg aatggttcag 720
ttggggtggg ggatcccctg gtncataaaa ngtcanaaag anggtacagg cggaacncca 780
agggtcgtcc tgcatttana ctcggaattt tggtgcc 817

<210> 604
<211> 694
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(694)
<223> n = A,T,C or G

<400> 604
cttttcaaat catttttnct cttctaggta tancctgtca ggtggcctaa tgtaattttt 60
gacatctcta ngaattttaa tagaaccaga aatgggtgcc agagatatgc ctgcactaat 120
cttaagtggg gatttatgta tttctcaagc aagtgattaa agcaaaacta ggcacgattg 180
aaatcaagat cttttaggca anaaagtcat gatgagtttt agaattattt taggactctg 240
tggctttctc ttcatagaaa tagaaaaaaa aattgtataa aaccacaaaa ggtcctgaat 300
agccaaagca acactganca aaaagaacan agcagggaag caacacacta ccngaattca 360
aattatacta ccagggtgta gtaaccaaaa cagcattcta ttggcataaa atagacacca 420
agaccaatgg ancagaataa agaaccccac aaataaatcc atatatntac cgccanctga 480
ttatcaataa cnaacaccaa gaacatatnt taagggacnt nctattcaat aantagtgct 540
ggnaaaaact gggaaatcca tatgcagaaa naatgaaact agacccctat ccctcaccat 600

acgcaaannt caacttcgga atgggattac aaaacttaag acattccaac ccaagaaact 660
atnaaancta ctattaagaa aacagatcnc nccc 694

<210> 605
<211> 678
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(678)
<223> n = A,T,C or G

<400> 605
taaaaatcta gactacacta ggaaattatt ttantatcag aagaatatca ggggtgtagt 60
actcatcana gctaaatgag agcgctttaa aaatgttagt ttgtcttccg ccatttctac 120
agaaagctgc aatttcaggt tttcaaccta ataggtgata tttaagaaaa aaaaaaagca 180
atcgcaaata gccccactgc ttttacaaat catttttct cttctaggta tagcctgtca 240
ggtggcctaa tgtaattttt gacatctcta ggaattttaa tagaaccaga aatgggtgcc 300
agagatatgc ctgcactaat cttaagtggg gatttatgta tttctcaagc aagtgattaa 360
agcaaaacta ggcacgattg aaatcaanat cttttaggca agaaagtcat gatgagtttt 420
anaattattt taggactctg tggctttctc ttcatagaaa tagaaaaaaa aaattgtata 480
aaaaccacaa aaggtcctga atagcccaaa gcaacactga acaaaangaa caaagcagga 540
agcaacacac taccggaatt caattatact accaaggtgt antaaccaaa acagcattct 600
attgggcata aaatagacca aagaccagtg ggaaacagaa taaagaancc caaaataaat 660
cctatattta cngcccnc 678

<210> 606
<211> 263
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(263)
<223> n = A,T,C or G

<400> 606
gtggggtcng cancagccaa ctcagcttcc tttcgggctt tgttagcaga cggatcatcc 60
tctagtccac tgtgntcaaa ttccattgtg tgggggccnc tcgcctcggc canagatctg 120
agtgancana cntgtcccca ctgaggtgcc ccacagcngn ttgtnttcag canggggctna 180
caactcgacc ggcagcgnan ggctggcaga antgngcgcc tnnctcattc ctacgcngtn 240
ngccgcagga aggangacag gcc 263

<210> 607
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 607
ccatgtgggt cccggttgtc tt 22

<210> 608
<211> 22
<212> DNA

<213> Artificial Sequence

<220>
<223> Primer

<400> 608
gataggggtg ctcaggggtt gg 22

<210> 609
<211> 40
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 609
gctggacagg gggcaaaagc tggggcagtg aaccatgtgc 40

<210> 610
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 610
ccttgtccag atagcccagt agctgac 27

<210> 611
<211> 46
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 611
gatagagaaa accgtccagg ccagtattgt gggaggctgg gagtgc 46

<210> 612
<211> 40
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 612
gcacatggtt cactgcccca gcttttgccc cctgtccagc 40

<210> 613
<211> 38
<212> DNA
<213> Artificial Sequence

<220>

<223> Primer

<400> 613
gccgctcgag ttagaattcg ggttggcca cgatggtg 38

<210> 614
<211> 53
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 614
cggcgggcat atgcatcacc atcaccatca catcataaac ggcgaggact gca 53

<210> 615
<211> 46
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 615
gcactcccag cctcccacaa tactggcctg gacggttttc tctatc 46

<210> 616
<211> 1350
<212> DNA
<213> Homo sapien

<400> 616
atgcatcacc atcaccatca catcataaac ggcgaggact gcagcccgca ctcgcagccc 60
tggcaggcgg cactggtcat ggaaaacgaa ttgttctgct cgggcgtcct ggtgcatccg 120
cagtgggtgc tgtcagccgc acactgtttc cagaactcct acaccatcgg gctgggcctg 180
cacagtcttg aggccgacca agagccaggg agccagatgg tggaggccag cctctccgta 240
cggcacccag agtacaacag acccttgctc gctaacgacc tcatgctcat caagttggac 300
gaatccgtgt ccgagtctga caccatccgg agcatcagca ttgcttcgca gtgccctacc 360
gcggggaact cttgcctcgt ttctggctgg ggtctgctgg cgaacggcag aatgcctacc 420
gtgctgcagt gcgtgaacgt gtcggtggtg tctgaggagg tctgcagtaa gctctatgac 480
ccgctgtacc accccagcat gttctgcgcc ggcggagggc aagaccagaa ggactcctgc 540
aacggtgact ctgggggccc cctgatctgc aacgggtact tgcagggcct tgtgtctttc 600
ggaaaagccc cgtgtggcca agttggcgtg ccaggtgtct acaccaacct ctgcaaattc 660
actgagtgga tagagaaaac cgtccaggcc agtattgtgg gaggctggga gtgcgagaag 720
cattcccaac cctggcaggt gcttgtggcc tctcgtggca gggcagtctg cggcggtgtt 780
ctggtgcacc cccagtgggt cctcacagct gcccactgca tcaggaacaa aagcgtgatc 840
ttgctgggtc ggcacagcct gtttcatcct gaagacacag gccaggtatt tcaggtcagc 900
cacagcttcc cacacccgct ctacgatatg agcctcctga agaatcgatt cctcaggcca 960
ggtgatgact ccagccacga cctcatgctg ctccgcctgt cagagcctgc cgagctcacg 1020
gatgctgtga aggtcatgga cctgcccacc caggagccag cactggggac cacctgctac 1080
gcctcaggct ggggcagcat tgaaccagag gagttcttga ccccaaagaa acttcagtgt 1140
gtggacctcc atgttatttc caatgacgtg tgtgcgcaag ttcaccctca gaaggtgacc 1200
aagttcatgc tgtgtgctgg acgctggaca gggggcaaaa gctggggcag tgaaccatgt 1260
gccctgcccg aaaggccttc cctgtacacc aaggtggtgc attaccggaa gtggatcaag 1320
gacaccatcg tggccaaccc cgaattctaa 1350

<210> 617

<211> 449
<212> PRT
<213> Homo sapien

<400> 617
Met His His His His His His Ile Ile Asn Gly Glu Asp Cys Ser Pro
1 5 10 15
His Ser Gln Pro Trp Gln Ala Ala Leu Val Met Glu Asn Glu Leu Phe
20 25 30
Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Ala His
35 40 45
Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu Glu
50 55 60
Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala Ser Leu Ser Val
65 70 75 80
Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu
85 90 95
Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile
100 105 110
Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu Val Ser
115 120 125
Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro Thr Val Leu Gln Cys
130 135 140
Val Asn Val Ser Val Val Ser Glu Glu Val Cys Ser Lys Leu Tyr Asp
145 150 155 160
Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly Gly Gly Gln Asp Gln
165 170 175
Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro Leu Ile Cys Asn Gly
180 185 190
Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala Pro Cys Gly Gln Val
195 200 205
Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys Phe Thr Glu Trp Ile
210 215 220
Glu Lys Thr Val Gln Ala Ser Ile Val Gly Gly Trp Glu Cys Glu Lys
225 230 235 240
His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala Val
245 250 255
Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala His
260 265 270
Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu Phe
275 280 285
His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe Pro
290 295 300
His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg Pro
305 310 315 320
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340 345 350
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355 360 365
Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu His
370 375 380
Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val Thr
385 390 395 400
Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Trp Gly
405 410 415
Ser Glu Pro Cys Ala Leu Pro Glu Arg Pro Ser Leu Tyr Thr Lys Val

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<210> 618
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<212> DNA
<213> Homo sapien

<400> 618

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<212> DNA
<213> Homo sapien

<400> 619

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<211> 2051
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(2051)
<223> n = A,T,C or G

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<212> DNA
<213> Homo sapien

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<223> n = A,T,C or G

<400> 621

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<212> DNA
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<220>
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<223> n = A,T,C or G

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Lys Lys Arg Ile Pro Arg Thr Tyr Pro Ser His Leu Trp Ile Pro Gly
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35 40 45

Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr
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Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro
65 70 75 80

Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu
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Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile
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Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys
115 120 125

Ser Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu
130 135 140

Asp Met Val Phe Met Pro Asp Glu Asp Glu Arg Lys Glu Tyr Ile Leu
145 150 155 160

Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys
165 170 175

Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys
180 185 190

Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp
195 200 205

Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys
210 215 220

Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly

225 230 235 240

Thr Ala Pro Tyr Lys Trp Thr Gly Ser Ala Pro Ile Leu Gln Gln Tyr
245 250 255

Tyr Asn Thr Lys Gln Ala Val Cys Phe Gly Gln Cys Trp Val Phe Ala
260 265 270

Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser
275 280 285

Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val
290 295 300

Asp Thr Tyr Val Asn Glu Asn Gly Lys Lys Ile Thr Ser Met Thr His
305 310 315 320

Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg
325 330 335

Pro Asp Leu Pro Lys Gly Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr
340 345 350

Pro Gln Glu Arg Ser Gln Gly Val Phe Cys Cys Gly Pro Ser Pro Leu
355 360 365

Thr Ala Ile Arg Lys Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe
370 375 380

Val Phe Ser Glu Val Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met
385 390 395 400

Val Asn Gly Gln Glu Glu Leu His Val Ile Ser Met Glu Thr Thr Ser
405 410 415

Ile Gly Lys Asn Ile Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg
420 425 430

Asp Ile Thr Tyr Glu Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg
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Gln Val Met Asp His Ala Phe Leu Leu Leu Ser Ser Glu Arg Glu His
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Arg Arg Pro Val Lys Glu Asn Phe Leu His Met Ser Val Gln Ser Asp
465 470 475 480

Asp Val Leu Leu Gly Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg
485 490 495

Lys Thr Ala Ala Leu Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu
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Gln Leu Tyr Thr Gly Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys
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Thr Ser Gln Ile Gln Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp
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Ile Arg Gly Phe Ile Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met
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Ala Ser Glu Val Phe Thr Ser Phe Gln Tyr Pro Glu Phe Ser Ile Glu
            580                 585                 590

Leu Pro Asn Thr Gly Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile
        595                 600                 605

Phe Lys Asn Thr Leu Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu
    610                 615                 620

Glu Ser Leu Gly Ile Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val
625                 630                 635                 640

Gln Pro Gly Glu Thr Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys
                645                 650                 655

Thr Gly Pro Lys Lys Phe Ile Val Lys Leu Ser Ser Lys Gln Val Lys
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Glu Ile Asn Ala Gln Lys Ile Val Leu Ile Thr Lys
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<212> PRT
<213> Homo sapiens

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Ser Pro Val Phe Arg Arg Gly Gln Val Phe His Leu Arg Leu Val Leu
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Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr
    50                  55                  60

Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro
65                  70                  75                  80

Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu
                85                  90                  95

Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile
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Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys
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Asp Met Val Phe Met Pro Asp Glu Asp Glu Arg Lys Glu Tyr Ile Leu
145 150 155 160

Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys
165 170 175

Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys
180 185 190

Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp
195 200 205

Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys
210 215 220

Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly
225 230 235 240

Thr Ala Pro Tyr Lys Trp Thr Gly Ser Ala Pro Ile Leu Gln Gln Tyr
245 250 255

Tyr Asn Thr Lys Gln Ala Val Cys Phe Gly Gln Cys Trp Val Phe Ala
260 265 270

Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser
275 280 285

Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val
290 295 300

Asp Thr Tyr Val Asn Glu Asn Gly Glu Lys Ile Thr Ser Met Thr His
305 310 315 320

Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg
325 330 335

Pro Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr Pro Gln Glu Arg Ser
340 345 350

Gln Gly Val Phe Cys Cys Gly Pro Ser Pro Leu Thr Ala Ile Arg Lys
355 360 365

Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe Val Phe Ser Glu Val
370 375 380

Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met Val Asn Gly Gln Glu
385 390 395 400

Glu Leu His Val Ile Ser Met Glu Thr Thr Ser Ile Gly Lys Asn Ile
405 410 415

Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg Asp Ile Thr Tyr Glu
420 425 430

Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg Gln Val Met Asp His

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Ala Phe Leu Leu Leu Ser Ser Glu Arg Glu His Arg Gln Pro Val Lys
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Glu Asn Phe Leu His Met Ser Val Gln Ser Asp Asp Val Leu Leu Gly
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Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg Lys Thr Ala Ala Leu
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Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu Gln Leu Tyr Thr Gly
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Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys Thr Ser Gln Ile Gln
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Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp Ser Lys Thr Tyr Ile
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Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val Ile Arg Gly Phe Ile
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Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met Ala Ser Glu Val Phe
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Thr Ser Asn Gln Tyr Pro Glu Phe Ser Ile Glu Leu Pro Asn Thr Gly
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Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile Phe Lys Asn Thr Leu
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Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu Glu Ser Leu Gly Ile
    610                 615                 620

Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val Gln Pro Gly Glu Thr
625                 630                 635                 640

Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys Thr Gly Pro Lys Lys
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35 40 45

Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
50 55 60

Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
65 70 75 80

Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
85 90 95

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Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser
            100                 105                 110

Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp
        115                 120                 125

His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys
    130                 135                 140

Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile
145                 150                 155                 160

Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His
                165                 170                 175

Tyr Gly Leu Thr Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile
            180                 185                 190

Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp
        195                 200                 205

Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu
    210                 215                 220

Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro
225                 230                 235                 240

Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn
                245                 250                 255

Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu
            260                 265                 270

Glu Lys His Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly
        275                 280                 285

Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly Lys Glu Thr Leu
    290                 295                 300

Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val
305                 310                 315                 320

Glu Gly Ser Gly Arg Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val
                325                 330                 335

Glu Asp Ala Pro Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe
            340                 345                 350

Leu Pro Arg Thr Val Ser Arg Leu Ser Glu Glu Glu Thr Glu Ser Trp
        355                 360                 365

Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val
    370                 375                 380

Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser
385                 390                 395                 400
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Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn
                405                 410                 415

Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu
            420                 425                 430

Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp
        435                 440                 445

Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe
    450                 455                 460

Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr
465                 470                 475                 480

His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val
                485                 490                 495

Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu
            500                 505                 510

Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys
        515                 520                 525

Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val
    530                 535                 540

Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile
545                 550                 555                 560

Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg
                565                 570                 575

Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu
            580                 585                 590

Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu
        595                 600                 605

Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr
    610                 615                 620

Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu
625                 630                 635                 640

Ala Trp Gly Gly Ser Asn Cys Leu Glu Leu Ala Val Glu Ala Thr Asp
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Gln His Phe Thr Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln
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Trp Tyr Gly Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu
        675                 680                 685

Cys Leu Phe Ile Ile Pro Leu Val Gly Cys Gly Phe Val Ser Phe Arg
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Lys Lys Pro Val Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala
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705 710 715 720

Phe Phe Thr Ser Pro Phe Val Val Phe Ser Trp Asn Val Val Phe Tyr
725 730 735

Ile Ala Phe Leu Leu Leu Phe Ala Tyr Val Leu Leu Met Asp Phe His
740 745 750

Ser Val Pro His Pro Pro Glu Leu Val Leu Tyr Ser Leu Val Phe Val
755 760 765

Leu Phe Cys Asp Glu Val Arg Gln Trp Tyr Val Asn Gly Val Asn Tyr
770 775 780

Phe Thr Asp Leu Trp Asn Val Met Asp Thr Leu Gly Leu Phe Tyr Phe
785 790 795 800

Ile Ala Gly Ile Val Phe Arg Leu His Ser Ser Asn Lys Ser Ser Leu
805 810 815

Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu
820 825 830

Arg Leu Ile His Ile Phe Thr Val Ser Arg Asn Leu Gly Pro Lys Ile
835 840 845

Ile Met Leu Gln Arg Met Leu Ile Asp Val Phe Phe Phe Leu Phe Leu
850 855 860

Phe Ala Val Trp Met Val Ala Phe Gly Val Ala Arg Gln Gly Ile Leu
865 870 875 880

Arg Gln Asn Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr
885 890 895

Glu Pro Tyr Leu Ala Met Phe Gly Gln Val Pro Ser Asp Val Asp Gly
900 905 910

Thr Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys
915 920 925

Pro Leu Cys Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu
930 935 940

Trp Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile
945 950 955 960

Leu Leu Val Asn Leu Leu Val Ala Met Phe Gly Tyr Thr Val Gly Thr
965 970 975

Val Gln Glu Asn Asn Asp Gln Val Trp Lys Phe Gln Arg Tyr Phe Leu
980 985 990

Val Gln Glu Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro Phe Ile Val
995 1000 1005

Phe Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe Lys Cys Cys Cys
1010 1015 1020

Lys Glu Lys Asn Met Glu Ser Ser Val Cys Cys Phe Lys Asn Glu Asp
1025 1030 1035 1040

Asn Glu Thr Leu Ala Trp Glu Gly Val Met Lys Glu Asn Tyr Leu Val
1045 1050 1055

Lys Ile Asn Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg
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Glu Ile Ala Asn Lys Ile Lys
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Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
50 55 60

Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
65 70 75 80

Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
85 90 95

Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser

100 105 110

Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp
115 120 125

His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys
130 135 140

Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile
145 150 155 160

Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His
165 170 175

Tyr Gly Leu Met Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile
180 185 190

Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp
195 200 205

Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu
210 215 220

Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro
225 230 235 240

Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn
245 250 255

Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu
260 265 270

Glu Lys Tyr Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly
275 280 285

Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly Lys Glu Thr Leu
290 295 300

Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val
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Glu Gly Ser Gly Gln Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val
325 330 335

Glu Asp Ala Leu Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe
340 345 350

Leu Pro Arg Thr Val Ser Arg Leu Pro Glu Glu Glu Thr Glu Ser Trp
355 360 365

Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val
370 375 380

Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser
385 390 395 400

Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn
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Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu
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Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp
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His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val
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Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu
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Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys
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Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val
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Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile
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Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg
565 570 575

Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu
580 585 590

Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu
595 600 605

Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr
610 615 620

Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu
625 630 635 640

Ala Trp Gly Gly Ser Asn Cys Leu Glu Leu Ala Val Glu Ala Thr Asp
645 650 655

Gln His Phe Ile Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln
660 665 670

Trp Tyr Gly Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu
675 680 685

Cys Leu Phe Ile Ile Pro Leu Val Gly Cys Gly Phe Val Ser Phe Arg
690 695 700

Lys Lys Pro Val Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala
705 710 715 720

Phe Phe Thr Ser Pro Phe Val Val Phe Ser Trp Asn Val Val Phe Tyr
725 730 735

Ile Ala Phe Leu Leu Leu Phe Ala Tyr Val Leu Leu Met Asp Phe His
740 745 750

Ser Val Pro His Pro Pro Glu Leu Val Leu Tyr Ser Leu Val Phe Val
755 760 765

Leu Phe Cys Asp Glu Val Arg Gln Trp Tyr Val Asn Gly Val Asn Tyr
770 775 780

Phe Thr Asp Leu Trp Asn Val Met Asp Thr Leu Gly Leu Phe Tyr Phe
785 790 795 800

Ile Ala Gly Ile Val Phe Arg Leu His Ser Ser Asn Lys Ser Ser Leu
805 810 815

Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu
820 825 830

Arg Leu Ile His Ile Phe Thr Val Ser Arg Asn Leu Gly Pro Lys Ile
835 840 845

Ile Met Leu Gln Arg Met Leu Ile Asp Val Phe Phe Phe Leu Phe Leu
850 855 860

Phe Ala Xaa Trp Met Val Ala Phe Gly Val Ala Arg Gln Gly Ile Leu
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Arg Gln Asn Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr
885 890 895

Glu Pro Tyr Leu Ala Met Phe Gly Gln Val Pro Ser Asp Val Asp Gly
900 905 910

Thr Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys
915 920 925

Pro Leu Cys Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu
930 935 940

Trp Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile
945 950 955 960

Leu Leu Val Asn Leu Leu Val Ala Met Phe Gly Tyr Thr Val Gly Thr
965 970 975

Val Gln Glu Asn Asn Asp Gln Val Trp Lys Phe Gln Arg Tyr Phe Leu
980 985 990

Val Gln Glu Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro Phe Ile Val
995 1000 1005

Phe Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe Lys Cys Cys Cys
1010 1015 1020

Lys Glu Lys Asn Met Glu Ser Ser Val Cys Cys Phe Lys Asn Glu Asp

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Asn Glu Thr Leu Ala Trp Glu Gly Val Met Lys Glu Asn Tyr Leu Val
1045 1050 1055

Lys Ile Asn Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg
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Glu Ile Ala Asn Lys Ile Lys
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<211> 15
<212> PRT
<213> Homo sapiens

<400> 665
Ala Leu Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val
5 10 15

<210> 666
<211> 17
<212> PRT
<213> Homo sapiens

<400> 666
Ser Gln Pro Trp Gln Ala Ala Leu Val Met Glu Asn Glu Leu Phe Cys
5 10 15

Ser

<210> 667
<211> 15
<212> PRT
<213> Homo sapiens

<400> 667
Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu
5 10 15

<210> 668
<211> 15
<212> PRT
<213> Homo sapiens

<400> 668
Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser
5 10 15

<210> 669
<211> 15
<212> PRT
<213> Homo sapiens

<400> 669
Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser
5 10 15

<210> 670
<211> 15
<212> PRT
<213> Homo sapiens

<400> 670
Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
5 10 15

<210> 671
<211> 15
<212> PRT
<213> Homo sapiens

<400> 671
Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu
5 10 15

<210> 672
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 672
ggaccagcat atgaggaaca gaaggaatga cactc 35

<210> 673
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 673
ccgctcgagt ccaccccaag cttcacagg 29

<210> 674
<211> 1959
<212> DNA
<213> Homo sapiens

<400> 674
atgaggaaca gaaggaatga cactctggac agcacccgga ccctgtactc cagcgcgtct 60
cggagcacag acttgtctta cagtgaaagc gacttggtga attttattca agcaaatttt 120
aagaaacgag aatgtgtctt ctttaccaaa gattccaagg ccacggagaa tgtgtgcaag 180
tgtggctatg cccagagcca gcacatggaa ggcacccaga tcaaccaaag tgagaaatgg 240
aactacaaga aacacaccaa ggaatttcct accgacgcct tggggatat tcagtttgag 300
acactgggga agaaagggaa gtatatacgt ctgtcctgcg acacggacgc ggaaatcctt 360
tacgagctgc tgacccagca ctggcacctg aaaacaccca acctggtcat ttctgtgacc 420
gggggcgcca agaacttcgc cctgaagccg cgcatgcgca agatcttcag ccggctcatc 480
tacatcgcgc agtccaaagg tgcttggatt ctcacgggag gcacccatta tggcctgatg 540
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gtggccattg gcatagcagc ttggggcatg gtctccaacc gggacaccct catcaggaat 660
tgcgatgctg agggctattt tttagcccag taccttatgg atgacttcac aagagatcca 720
ctgtatatcc tggacaacaa ccacacacat ttgctgctcg tggacaatgg ctgtcatgga 780
catcccactg tcgaagcaaa gctccggaat cagctagaga agtatatctc tgagcgcact 840
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cagatcgcca agaattccta taatgatgcc ctcctcacgt ttgtctggaa actggttgcg 1560
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cttcagaata agaaggaact ctccaaagtc atttgggagc agaccagggg ctgcactctg 1740
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gctgctgggg agtccgagga gctggctaat gagtacgaga cccgggctgt tgagctgttc 1860
actgagtgtt acagcagcga tgaagacttg gcagaacagc tgctggtcta ttcctgtgaa 1920
gcttggggtg gactcgagca ccaccaccac caccactga 1959

<210> 675
<211> 652
<212> PRT
<213> Homo sapiens

<400> 675
Met Arg Asn Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr
5 10 15

Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu
20 25 30

Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
35 40 45

Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
50 55 60

```
Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
 65                  70                  75                  80

Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
                 85                  90                  95

Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser
            100                 105                 110

Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp
        115                 120                 125

His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys
    130                 135                 140

Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile
145                 150                 155                 160

Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His
                165                 170                 175

Tyr Gly Leu Met Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile
            180                 185                 190

Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp
        195                 200                 205

Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu
    210                 215                 220

Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro
225                 230                 235                 240

Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn
                245                 250                 255

Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu
            260                 265                 270

Glu Lys Tyr Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly
        275                 280                 285

Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly Lys Glu Thr Leu
    290                 295                 300

Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val
305                 310                 315                 320

Glu Gly Ser Gly Gln Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val
                325                 330                 335

Glu Asp Ala Leu Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe
            340                 345                 350

Leu Pro Arg Thr Val Ser Arg Leu Pro Glu Glu Glu Thr Glu Ser Trp
        355                 360                 365

Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val
```

370 375 380

Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser
385 390 395 400

Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn
405 410 415

Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu
420 425 430

Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp
435 440 445

Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe
450 455 460

Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr
465 470 475 480

His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val
485 490 495

Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu
500 505 510

Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys
515 520 525

Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val
530 535 540

Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile
545 550 555 560

Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg
565 570 575

Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu
580 585 590

Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu
595 600 605

Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr
610 615 620

Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu
625 630 635 640

Ala Trp Gly Gly Leu Glu His His His His His His
645 650

<210> 676
<211> 132

<212> PRT
<213> Homo sapien

<400> 676
Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
1 5 10 15
Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser
20 25 30
Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly
35 40 45
Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val
50 55 60
Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val
65 70 75 80
Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala
85 90 95
Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp
100 105 110
Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu
115 120 125
Gly Pro Pro Ala
130

<210> 677
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 677
ggggaattca tgatccggga gaaatttgcc cactgc 36

<210> 678
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 678
gggctcgagt caggagtttg agaccagcct ggc 33

<210> 679
<211> 675
<212> DNA
<213> Homo sapiens

<400> 679
atgcatcacc atcaccatca cacggccgcg tccgataact tccagctgtc ccagggtggg 60
cagggattcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120

accgttcata tcgggcctac cgccttcctc ggcttgggtg ttgtcgacaa caacggcaac 180
ggcgcacgag tccaacgcgt ggtcgggagc gctccggcgg caagtctcgg catctccacc 240
ggcgacgtga tcaccgcggt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300
gcgcttaacg ggcatcatcc cggtgacgtc atctcggtga cctggcaaac caagtcgggc 360
ggcacgcgta cagggaacgt gacattggcc gagggacccc cggccgaatt catgatccgg 420
gagaaatttg cccactgcac cgtgctaacc attgcacaca gattgaacac cattattgac 480
agcgacaaga taatggtttt agattcagga agactgaaag aatatgatga gccgtatgtt 540
ttgctgcaaa ataaagagag cctattttac aagatggtgc aacaactggg caaggcagaa 600
gccgctgccc tcactgaaac agcaaaacag agatggggtt tcaccatgtt ggccaggctg 660
gtctcaaact cctga 675

<210> 680
<211> 291
<212> DNA
<213> Homo sapiens

<400> 680
atggggatcc gggagaaatt tgcccactgc accgtgctaa ccattgcaca cagattgaac 60
accattattg acagcgacaa gataatggtt ttagattcag gaagactgaa agaatatgat 120
gagccgtatg ttttgctgca aaataaagag agcctatttt acaagatggt gcaacaactg 180
ggcaaggcag aagccgctgc cctcactgaa acagcaaaac agagatgggg tttcaccatg 240
ttggccaggc tggtctcaaa ctccctcgag caccaccacc accaccactg a 291

<210> 681
<211> 1074
<212> DNA
<213> Homo sapiens

<400> 681
atgtcagcca ttgagagggt gtcagaggca atcgtcagca tccgaagaat ccagaccttt 60
ttgctacttg atgagatatc acagcgcaac cgtcagctgc cgtcagatgg taaaaagatg 120
gtgcatgtgc aggattttac tgctttttgg gataaggcat cagagacccc aactctacaa 180
ggcctttcct ttactgtcag acctggcgaa ttgttagctg tggtcggccc cgtgggagca 240
gggaagtcat cactgttaag tgccgtgctc ggggaattgg ccccaagtca cgggctggtc 300
agcgtgcatg gaagaattgc ctatgtgtct cagcagccct gggtgttctc gggaactctg 360
aggagtaata ttttatttgg gaagaaatac gaaaaggaac gatatgaaaa agtcataaag 420
gcttgtgctc tgaaaaagga tttacagctg ttggaggatg gtgatctgac tgtgatagga 480
gatcggggaa ccacgctgag tggagggcag aaagcacggg taaaccttgc aagagcagtg 540
tatcaagatg ctgacatcta tctcctggac gatcctctca gtgcagtaga tgcggaagtt 600
agcagacact tgttcgaact gtgtatttgt caaattttgc atgagaagat cacaatttta 660
gtgactcatc agttgcagta cctcaaagct gcaagtcaga ttctgatatt gaaagatggt 720
aaaatggtgc agaaggggac ttacactgag ttcctaaaat ctggtataga ttttggctcc 780
cttttaaaga aggataatga ggaaagtgaa caacctccag ttccaggaac tcccacacta 840
aggaatcgta ccttctcaga gtcttcggtt tggtctcaac aatcttctag accctccttg 900
aaagatggtg ctctggagag ccaagataca gagaatgtcc cagttacact atcagaggag 960
aaccgttctg aaggaaaagt tggttttcag gcctataaga attacttcag agctggtgct 1020
cactggattg tcttcatttt ccttattctc gagcaccacc accaccacca ctga 1074

<210> 682
<211> 224
<212> PRT
<213> Homo sapiens

<400> 682
Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu
5 10 15

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala

```
            20                  25                  30

Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala
        35                  40                  45

Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val
    50                  55                  60

Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr
65                  70                  75                  80

Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr
                85                  90                  95

Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser
            100                 105                 110

Val Thr Trp Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr
        115                 120                 125

Leu Ala Glu Gly Pro Pro Ala Glu Phe Met Ile Arg Glu Lys Phe Ala
    130                 135                 140

His Cys Thr Val Leu Thr Ile Ala His Arg Leu Asn Thr Ile Ile Asp
145                 150                 155                 160

Ser Asp Lys Ile Met Val Leu Asp Ser Gly Arg Leu Lys Glu Tyr Asp
                165                 170                 175

Glu Pro Tyr Val Leu Leu Gln Asn Lys Glu Ser Leu Phe Tyr Lys Met
            180                 185                 190

Val Gln Gln Leu Gly Lys Ala Glu Ala Ala Ala Leu Thr Glu Thr Ala
        195                 200                 205

Lys Gln Arg Trp Gly Phe Thr Met Leu Ala Arg Leu Val Ser Asn Ser
    210                 215                 220
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<210> 683
<211> 357
<212> PRT
<213> Homo sapiens

<400> 683

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Met Ser Ala Ile Glu Arg Val Ser Glu Ala Ile Val Ser Ile Arg Arg
                5                   10                  15

Ile Gln Thr Phe Leu Leu Leu Asp Glu Ile Ser Gln Arg Asn Arg Gln
            20                  25                  30

Leu Pro Ser Asp Gly Lys Lys Met Val His Val Gln Asp Phe Thr Ala
        35                  40                  45

Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr Leu Gln Gly Leu Ser Phe
```

```
    50                  55                  60

Thr Val Arg Pro Gly Glu Leu Leu Ala Val Val Gly Pro Val Gly Ala
65                  70                  75                  80

Gly Lys Ser Ser Leu Leu Ser Ala Val Leu Gly Glu Leu Ala Pro Ser
                85                  90                  95

His Gly Leu Val Ser Val His Gly Arg Ile Ala Tyr Val Ser Gln Gln
            100                 105                 110

Pro Trp Val Phe Ser Gly Thr Leu Arg Ser Asn Ile Leu Phe Gly Lys
        115                 120                 125

Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val Ile Lys Ala Cys Ala Leu
    130                 135                 140

Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly Asp Leu Thr Val Ile Gly
145                 150                 155                 160

Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn Leu
                165                 170                 175

Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile Tyr Leu Leu Asp Asp Pro
            180                 185                 190

Leu Ser Ala Val Asp Ala Glu Val Ser Arg His Leu Phe Glu Leu Cys
        195                 200                 205

Ile Cys Gln Ile Leu His Glu Lys Ile Thr Ile Leu Val Thr His Gln
    210                 215                 220

Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile Leu Ile Leu Lys Asp Gly
225                 230                 235                 240

Lys Met Val Gln Lys Gly Thr Tyr Thr Glu Phe Leu Lys Ser Gly Ile
                245                 250                 255

Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn Glu Glu Ser Glu Gln Pro
            260                 265                 270

Pro Val Pro Gly Thr Pro Thr Leu Arg Asn Arg Thr Phe Ser Glu Ser
        275                 280                 285

Ser Val Trp Ser Gln Gln Ser Ser Arg Pro Ser Leu Lys Asp Gly Ala
    290                 295                 300

Leu Glu Ser Gln Asp Thr Glu Asn Val Pro Val Thr Leu Ser Glu Glu
305                 310                 315                 320

Asn Arg Ser Glu Gly Lys Val Gly Phe Gln Ala Tyr Lys Asn Tyr Phe
                325                 330                 335

Arg Ala Gly Ala His Trp Ile Val Phe Ile Phe Leu Ile Leu Glu His
            340                 345                 350

His His His His His
        355
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<210> 684
<211> 96
<212> PRT
<213> Homo sapiens

<400> 684
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Met Gly Ile Arg Glu Lys Phe Ala His Cys Thr Val Leu Thr Ile Ala
                5                   10                  15

His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys Ile Met Val Leu Asp
            20                  25                  30

Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr Val Leu Leu Gln Asn
        35                  40                  45

Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln Leu Gly Lys Ala Glu
    50                  55                  60

Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln Arg Trp Gly Phe Thr Met
65                  70                  75                  80

Leu Ala Arg Leu Val Ser Asn Ser Leu Glu His His His His His His
                85                  90                  95
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<210> 685
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 685
cgcccatggg gatccgggag aaatttgccc actgc 35

<210> 686
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 686
cgcctcgagg gagtttgaga ccagcctggc caaca 35

<210> 687
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 687
gcatggacca tatgtcagcc attgagaggg tgtcagag 38

<210> 688
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 688
ccgctcgaga ataaggaaaa tgaagacaat ccag 34

<210> 689
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 689
gttgaattca tgcacgggcc ccaggtg 27

<210> 690
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 690
cccctcgagt cactatggtc tgcctcttga 30

<210> 691
<211> 915
<212> DNA
<213> Homo sapiens

<400> 691
atgcatcacc atcaccatca cacggccgcg tccgataact tccagctgtc ccagggtggg 60
cagggattcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120
accgttcata tcgggcctac cgccttcctc ggcttgggtg ttgtcgacaa caacggcaac 180
ggcgcacgag tccaacgcgt ggtcgggagc gctccggcgg caagtctcgg catctccacc 240
ggcgacgtga tcaccgcggt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300
gcgcttaacg ggcatcatcc cggtgacgtc atctcggtga cctggcaaac caagtcgggc 360
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ccccaggtgc tggcacgctg ctccgagtgt gcttgtcctg ccttggctgc cacctctgcg 480
ggggtgcgtc tggagggggt ggaccggcca ccaaccttac ccagtcaagg aagtggatgg 540
ccatgttccc acagcctgag tggctgccac ctgatggctg atggagcaaa ggccttagga 600
aaagcagatg gcccttggcc ctaccttttt gttagaagaa ctgatgttcc atgtcctgca 660
gcgagtgagg ttggtggctg tgcccccagc tcctggcgcg ccctcgcaga ggtgactggt 720

tgctctttgg gccctcttgg ccttgcccag catgcacaag cctcagtgct actactgtgc 780
tacaaatgga gccatatagg ggaaacgagc agccatctca ggagcaaggt gtatgctgcc 840
tttgggggct ccagtccttg cctcaagggt cttatgtcac tgtgggcttc ttggttgtca 900
agaggcagac catag 915

<210> 692
<211> 304
<212> PRT
<213> Homo sapiens

<400> 692
Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu
5 10 15

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala
20 25 30

Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala
35 40 45

Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val
50 55 60

Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr
65 70 75 80

Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr
85 90 95

Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser
100 105 110

Val Thr Trp Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr
115 120 125

Leu Ala Glu Gly Pro Pro Ala Glu Phe Met His Gly Pro Gln Val Leu
130 135 140

Ala Arg Cys Ser Glu Cys Ala Cys Pro Ala Leu Ala Ala Thr Ser Ala
145 150 155 160

Gly Val Arg Leu Glu Gly Val Asp Arg Pro Pro Thr Leu Pro Ser Gln
165 170 175

Gly Ser Gly Trp Pro Cys Ser His Ser Leu Ser Gly Cys His Leu Met
180 185 190

Ala Asp Gly Ala Lys Ala Leu Gly Lys Ala Asp Gly Pro Trp Pro Tyr
195 200 205

Leu Phe Val Arg Arg Thr Asp Val Pro Cys Pro Ala Ala Ser Glu Val
210 215 220

Gly Gly Cys Ala Pro Ser Ser Trp Arg Ala Leu Ala Glu Val Thr Gly
225 230 235 240

Cys Ser Leu Gly Pro Leu Gly Leu Ala Gln His Ala Gln Ala Ser Val
245 250 255

```
Leu Leu Leu Cys Tyr Lys Trp Ser His Ile Gly Glu Thr Ser Ser His
            260                 265                 270

Leu Arg Ser Lys Val Tyr Ala Ala Phe Gly Gly Ser Ser Pro Cys Leu
        275                 280                 285

Lys Gly Leu Met Ser Leu Trp Ala Ser Trp Leu Ser Arg Gly Arg Pro
    290                 295                 300
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<210> 693
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 693
cgaagtcacg tggaggccag cctc 24

<210> 694
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 694
cctgaccgaa ttcattaact ggcctggac 29

<210> 695
<211> 166
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> (1)...(166)
<223> Xaa = Any Amino Acid

<400> 695

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Met Gly His His His His His His Val Glu Ala Ser Leu Ser Val Arg
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His Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile
            20                  25                  30
Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser
        35                  40                  45
Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu Val Ser Gly
    50                  55                  60
Trp Gly Leu Leu Ala Asn Gly Arg Met Pro Thr Val Leu Gln Cys Val
65                  70                  75                  80
Asn Val Ser Val Val Ser Glu Glu Val Cys Ser Lys Leu Tyr Asp Pro
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```
                85                  90                  95
Leu Tyr His Pro Ser Met Phe Cys Ala Gly Gly Gly Gln Xaa Gln Xaa
            100                 105                 110
Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro Leu Ile Cys Asn Gly Tyr
        115                 120                 125
Leu Gln Gly Leu Val Ser Phe Gly Lys Ala Pro Cys Gly Gln Val Gly
    130                 135                 140
Val Pro Gly Val Tyr Thr Asn Leu Cys Lys Phe Thr Glu Trp Ile Glu
145                 150                 155                 160
Lys Thr Val Gln Ala Ser
                165

<210> 696
<211> 504
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(504)
<223> n = A,T,C or G

<400> 696
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aacagaccct tgctcgctaa cgacctcatg ctcatcaagt tggacgaatc cgtgtccgag     120
tctgacacca tccggagcat cagcattgct tcgcagtgcc ctaccgcggg gaactcttgc     180
ctcgtttctg gctggggtct gctggcgaac ggcagaatgc ctaccgtgct gcagtgcgtg     240
aacgtgtcgg tggtgtctga ggaggtctgc agtaagctct atgacccgct gtaccacccc     300
agcatgttct gcgccggcgg agggcaanac cagaangact cctgcaacgg tgactctggg     360
gggcccctga tctgcaacgg gtacttgcag ggccttgtgt ctttcggaaa agccccgtgt     420
ggccaagttg gcgtgccagg tgtctacacc aacctctgca aattcactga gtggatagag     480
aaaaccgtcc aggccagtta atga                                            504


<210> 697
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 697
ctcagggttc cggagccgcg g                                                21

<210> 698
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 698
ctatagaatt cattaccaaa aagctgggct ccagc                                 35


<210> 699
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<211> 241
<212> PRT
<213> Homo sapiens

<400> 699
Met Gln His His His His His His Leu Arg Val Pro Glu Pro Arg Pro
1   5   10   15
Gly Glu Ala Lys Ala Glu Gly Ala Ala Pro Pro Thr Pro Ser Lys Pro
            20   25   30
Leu Thr Ser Phe Leu Ile Gln Asp Ile Leu Arg Asp Gly Ala Gln Arg
        35   40   45
Gln Gly Gly Arg Thr Ser Ser Gln Arg Gln Arg Asp Pro Glu Pro Glu
    50   55   60
Pro Glu Pro Glu Pro Glu Gly Gly Arg Ser Arg Ala Gly Ala Gln Asn
65   70   75   80
Asp Gln Leu Ser Thr Gly Pro Arg Ala Ala Pro Glu Glu Ala Glu Thr
                85   90   95
Leu Ala Glu Thr Glu Pro Glu Arg His Leu Gly Ser Tyr Leu Leu Asp
            100   105   110
Ser Glu Asn Thr Ser Gly Ala Leu Pro Arg Leu Pro Gln Thr Pro Lys
        115   120   125
Gln Pro Gln Lys Arg Ser Arg Ala Ala Phe Ser His Thr Gln Val Ile
    130   135   140
Glu Leu Glu Arg Lys Phe Ser His Gln Lys Tyr Leu Ser Ala Pro Glu
145   150   155   160
Arg Ala His Leu Ala Lys Asn Leu Lys Leu Thr Glu Thr Gln Val Lys
                165   170   175
Ile Trp Phe Gln Asn Arg Arg Tyr Lys Thr Lys Arg Lys Gln Leu Ser
            180   185   190
Ser Glu Leu Gly Asp Leu Glu Lys His Ser Ser Leu Pro Ala Leu Lys
        195   200   205
Glu Glu Ala Phe Ser Arg Ala Ser Leu Val Ser Val Tyr Asn Ser Tyr
    210   215   220
Pro Tyr Tyr Pro Tyr Leu Tyr Cys Val Gly Ser Trp Ser Pro Ala Phe
225   230   235   240
Trp

<210> 700
<211> 729
<212> DNA
<213> Homo sapiens

<400> 700
atgcagcatc accaccatca ccacctcagg gttccggagc cgcggcccgg ggaggcgaaa 60
gcggaggggg ccgcgccgcc gaccccgtcc aagccgctca cgtccttcct catccaggac 120
atcctgcggg acggcgcgca gcggcaaggc ggccgcacga gcagccagag acagcgcgac 180
ccggagccgg agccagagcc agagccagag ggaggacgca gccgcgccgg ggcgcagaac 240
gaccagctga gcaccgggcc ccgcgccgcg ccggatgagg ccgagacgct ggcagagacc 300
gagccagaaa ggcacttggg gtcttatctg ttggactctg aaaacacttc aggcgccctt 360
ccaaggcttc cccaaacccc taagcagccg cagaagcgct cccgagctgc cttctcccac 420
actcaggtga tcgagttgga gaggaagttc agccatcaga agtacctgtc ggcccctgaa 480
cgggcccacc tggccaagaa cctcaagctc acggagaccc aagtgaagat atggttccag 540
aacagacgct ataagactaa gcgaaagcag ctctcctcgg agctgggaga cttggagaag 600
cactcctttt tgccggccct gaaagaggag gccttctccc gggcctccct ggtctccgtg 660
tataacagct atccttacta cccatacctg cactgcgtgg gcagctggag cccagctttt 720
tggtaatga 729

<210> 701
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 701
ctactaagcg ctggagtgag ggatcag 27

<210> 702
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 702
catcgagaat tcactactct ctgactagat gtc 33

<210> 703
<211> 161
<212> PRT
<213> Homo sapiens

<400> 703
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Met Gln His His His His His His Ala Gly Val Arg Asp Gln Gly Gln
 1               5                  10                  15
Gly Ala Arg Trp Pro His Thr Gly Lys Arg Gly Pro Leu Leu Gln Gly
            20                  25                  30
Leu Thr Trp Ala Thr Gly Gly His Cys Phe Ser Ser Glu Glu Ser Gly
        35                  40                  45
Ala Val Asp Gly Ala Gly Gln Lys Lys Asp Arg Ala Trp Leu Arg Cys
    50                  55                  60
Pro Glu Ala Val Ala Gly Phe Pro Leu Gly Ser Asp Cys Arg Glu Gly
65                  70                  75                  80
Gly Arg Gln Gly Cys Gly Gly Ser Asp Asp Glu Asp Asp Leu Gly Val
                85                  90                  95
Ala Pro Gly Leu Ala Pro Ala Trp Ala Leu Thr Gln Pro Pro Ser Gln
            100                 105                 110
Ser Pro Gly Pro Gln Ser Leu Pro Ser Thr Pro Ser Ser Ile Trp Pro
        115                 120                 125
Gln Trp Val Ile Leu Ile Thr Glu Leu Thr Ile Pro Ser Pro Ala His
    130                 135                 140
Gly Pro Pro Trp Leu Pro Asn Ala Leu Glu Arg Gly His Leu Val Arg
145                 150                 155                 160
Glu
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<210> 704
<211> 489
<212> DNA
<213> Homo sapiens

<400> 704
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cctcacacag ggaagagagg gcccctcctg cagggcctca cctgggccac aggaggacac 120
tgcttttcct ctgaggagtc aggagctgtg gatggtgctg gacagaagaa ggacagggcc 180
tggctcaggt gtccagaggc tgtcgctggc ttccctttgg gatcagactg cagggaggga 240
gggcggcagg gttgtggggg gagtgacgat gaggatgacc tgggggtggc tccaggcctt 300
gcccctgcct gggccctcac ccagcctccc tcacagtctc ctggccctca gtctctcccc 360
tccactccat cctccatctg gcctcagtgg gtcattctga tcactgaact gaccataccc 420
agccctgccc acggccctcc atggctcccc aatgccctgg agaggggaca tctagtcaga 480
gagtagtga 489

<210> 705
<211> 132
<212> PRT
<213> Homo sapiens

<400> 705
Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
1 5 10 15
Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser
20 25 30
Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly
35 40 45
Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val
50 55 60
Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val
65 70 75 80
Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala
85 90 95
Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp
100 105 110
Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu
115 120 125
Gly Pro Pro Ala
130

<210> 706
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 706
ggggaattca tcacctatgt gccgcctctg c 31

<210> 707
<211> 40
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 707
gggctcgagt cactcgccca cgaaatccgt gtaaaacagc 40

<210> 708
<211> 1203
<212> DNA
<213> Homo sapiens

<400> 708
atgcatcacc atcaccatca cacggccgcg tccgataact tccagctgtc ccagggtggg 60
cagggattcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120
accgttcata tcgggcctac cgccttcctc ggcttgggtg ttgtcgacaa caacggcaac 180
ggcgcacgag tccaacgcgt ggtcgggagc gctccggcgg caagtctcgg catctccacc 240
ggcgacgtga tcaccgcggt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300
gcgcttaacg ggcatcatcc cggtgacgtc atctcggtga cctggcaaac caagtcgggc 360
ggcacgcgta cagggaacgt gacattggcc gagggacccc cggccgaatt catcacctat 420
gtgccgcctc tgctgctgga agtgggggta gaggagaagt tcatgaccat ggtgctgggc 480
attggtccag tgctgggcct ggtctgtgtc ccgctcctag gctcagccag tgaccactgg 540
cgtggacgct atggccgccg ccggcccttc atctgggcac tgtccttggg catcctgctg 600
agcctctttc tcatcccaag ggccggctgg ctagcagggc tgctgtgccc ggatcccagg 660
cccctggagc tggcactgct catcctgggc gtggggctgc tggacttctg tggccaggtg 720
tgcttcactc cactggaggc cctgctctct gacctcttcc gggacccgga ccactgtcgc 780
caggcctact ctgtctatgc cttcatgatc agtcttgggg gctgcctggg ctacctcctg 840
cctgccattg actgggacac cagtgccctg gcccccctacc tgggcaccca ggaggagtgc 900
ctctttggcc tgctcaccct catcttcctc acctgcgtag cagccacact gctggtggct 960
gaggaggcag cgctgggccc caccgagcca gcagaagggc tgtcggcccc ctccttgtcg 1020
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cggctgcacc agctgtgctg ccgcatgccc cgcaccctgc gccggctctt cgtggctgag 1140
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tga 1203

<210> 709
<211> 400
<212> PRT
<213> Homo sapiens

<400> 709
Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu
5 10 15

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala
20 25 30

Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala
35 40 45

Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val
50 55 60

Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr
65 70 75 80

Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr
85 90 95

Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser

100 105 110

Val Thr Trp Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr
115 120 125

Leu Ala Glu Gly Pro Pro Ala Glu Phe Ile Thr Tyr Val Pro Pro Leu
130 135 140

Leu Leu Glu Val Gly Val Glu Glu Lys Phe Met Thr Met Val Leu Gly
145 150 155 160

Ile Gly Pro Val Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala
165 170 175

Ser Asp His Trp Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp
180 185 190

Ala Leu Ser Leu Gly Ile Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala
195 200 205

Gly Trp Leu Ala Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu
210 215 220

Ala Leu Leu Ile Leu Gly Val Gly Leu Leu Asp Phe Cys Gly Gln Val
225 230 235 240

Cys Phe Thr Pro Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro
245 250 255

Asp His Cys Arg Gln Ala Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu
260 265 270

Gly Gly Cys Leu Gly Tyr Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser
275 280 285

Ala Leu Ala Pro Tyr Leu Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu
290 295 300

Leu Thr Leu Ile Phe Leu Thr Cys Val Ala Ala Thr Leu Leu Val Ala
305 310 315 320

Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala
325 330 335

Pro Ser Leu Ser Pro His Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe
340 345 350

Arg Asn Leu Gly Ala Leu Leu Pro Arg Leu His Gln Leu Cys Cys Arg
355 360 365

Met Pro Arg Thr Leu Arg Arg Leu Phe Val Ala Glu Leu Cys Ser Trp
370 375 380

Met Ala Leu Met Thr Phe Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu
385 390 395 400

<210> 710
<211> 20
<212> PRT
<213> Homo sapiens

<400> 710
Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser Ala Cys Asp Val
5 10 15

Ser Val Arg Val
20

<210> 711
<211> 60
<212> DNA
<213> Homo sapiens

<400> 711
ctgctcccac ctccacccgc gctctgcggg gcctctgcct gtgatgtctc cgtacgtgtg 60

<210> 712
<211> 10
<212> PRT
<213> Homo sapiens

<400> 712
Ala Ser Ala Cys Asp Val Ser Val Arg Val
5 10

<210> 713
<211> 30
<212> DNA
<213> Homo sapiens

<400> 713
gcctctgcct gtgatgtctc cgtacgtgtg 30

<210> 714
<211> 9
<212> PRT
<213> Homo sapiens

<400> 714
Ala Ser Ala Cys Asp Val Ser Val Arg
1 5

<210> 715
<211> 9
<212> PRT
<213> Homo sapiens

<400> 715
Ser Ala Cys Asp Val Ser Val Arg Val
5

<210> 716
<211> 27

<212> DNA
<213> Homo sapiens

<400> 716
tctgcctgtg atgtctccgt acgtgtg 27

<210> 717
<211> 19
<212> PRT
<213> Homo sapiens

<400> 717
Gly Ile Gly Pro Val Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser
5 10 15

Ala Ser Asp

<210> 718
<211> 19
<212> PRT
<213> Homo sapiens

<400> 718
Val Pro Pro Leu Leu Leu Glu Val Gly Val Glu Glu Lys Phe Met Thr
5 10 15

Met Val Leu

<210> 719
<211> 19
<212> PRT
<213> Homo sapiens

<400> 719
Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala
5 10 15

Gln Leu Leu

<210> 720
<211> 57
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(57)
<223> n = A,T,C or G

<400> 720
ggnathggnc cngtnytngg nytngtntgy gtnccnytny tnggnwsngc nwsngay 57

<210> 721
<211> 57
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(57)
<223> n = A,T,C or G

<400> 721
gtnccnccny tnytnytnga rgtnggngtn gargaraart tyatgacnat ggtnytn 57

<210> 722
<211> 57
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(57)
<223> n = A,T,C or G

<400> 722
atggtncarm gnytntgggt nwsnmgnytn ytnmgncaym gnaargcnca rytnytn 57

<210> 723
<211> 9
<212> PRT
<213> Homo sapiens

<400> 723
Val Leu Gln Cys Val Asn Val Ser Val
1 5

<210> 724
<211> 9
<212> PRT
<213> Homo sapiens

<400> 724
Arg Met Pro Thr Val Leu Gln Cys Val
1 5

<210> 725
<211> 9
<212> PRT
<213> Homo sapiens

<400> 725
Asn Leu Cys Lys Phe Thr Glu Trp Ile
1 5

<210> 726
<211> 9
<212> PRT

<213> Homo sapiens

<400> 726
Met Leu Ile Lys Leu Asp Glu Ser Val
1 5

<210> 727
<211> 9
<212> PRT
<213> Homo sapiens

<400> 727
Leu Leu Ala Asn Asp Leu Met Leu Ile
1 5

<210> 728
<211> 10
<212> PRT
<213> Homo sapiens

<400> 728
Leu Leu Ala Asn Gly Arg Met Pro Thr Val
1 5 10

<210> 729
<211> 10
<212> PRT
<213> Homo sapiens

<400> 729
Leu Met Leu Ile Lys Leu Asp Glu Ser Val
1 5 10

<210> 730
<211> 10
<212> PRT
<213> Homo sapiens

<400> 730
Val Leu Gln Cys Val Asn Val Ser Val Val
1 5 10

<210> 731
<211> 10
<212> PRT
<213> Homo sapiens

<400> 731
Gly Leu Leu Ala Asn Gly Arg Met Pro Thr
1 5 10

<210> 732
<211> 10
<212> PRT
<213> Homo sapiens

<400> 732
Thr Val Leu Gln Cys Val Asn Val Ser Val

1 5 10

<210> 733
<211> 9
<212> PRT
<213> Homo sapiens

<400> 733
Gly Val Leu Val His Pro Gln Trp Val
1 5

<210> 734
<211> 9
<212> PRT
<213> Homo sapiens

<400> 734
Val Leu Val His Pro Gln Trp Val Leu
1 5

<210> 735
<211> 1195
<212> DNA
<213> Homo sapiens

<400> 735
ccgagactca cggtcaagct aaggcgaaga gtgggtggct gaagccatac tattttatag 60
aattaatgga aagcagaaaa gacatcacaa accaagaaga actttggaaa atgaagccta 120
ggagaaattt agaagaagac gattatttgc ataaggacac gggagagacc agcatgctaa 180
aaagacctgt gcttttgcat ttgcaccaaa cagcccatgc tgatgaattt gactgccctt 240
cagaacttca gcacacacag gaactctttc cacagtggca cttgccaatt aaaatagctg 300
ctattatagc atctctgact ttctttaca ctcttctgag ggaagtaatt cacccttag 360
caacttccca tcaacaatat ttttataaaa ttccaatcct ggtcatcaac aaagtcttgc 420
caatggtttc catcactctc ttggcattgg tttacctgcc aggtgtgata gcagcaattg 480
tccaacttca taatggaacc aagtataaga agtttccaca ttggttggat aagtggatgt 540
taacaagaaa gcagtttggg cttctcagtt tctttttgc tgtactgcat gcaatttata 600
gtctgtctta cccaatgagg cgatcctaca gatacaagtt gctaaactgg gcatatcaac 660
aggtccaaca aaataaagaa gatgcctgga ttgagcatga tgtttggaga atggagattt 720
atgtgtctct gggaattgtg ggattggcaa tactggctct gttggctgtg acatctattc 780
catctgtgag tgactctttg acatggagag aatttcacta tattcagagc aagctaggaa 840
ttgtttccct tctactgggc acaatacacg cattgatttt tgcctggaat aagtggatag 900
atataaaaca atttgtatgg tatacacctc caacttttat gatagctgtt ttccttccaa 960
ttgttgtcct gatatttaaa agcatactat tcctgccatg cttgaggaag aagatactga 1020
agattagaca tggttgggaa gacgtcacca aaattaacaa aactgagata tgttcccagt 1080
tgtagaatta ctgtttacac acatttttgt tcaatattga tatattttat caccaacatt 1140
tcaagtttgt atttgttaat aaaatgatta ttcaaggaaa aaaaaaaaaa aaaaa 1195

<210> 736
<211> 339
<212> PRT
<213> Homo sapiens

<400> 736
Met Glu Ser Arg Lys Asp Ile Thr Asn Gln Glu Glu Leu Trp Lys Met
5 10 15

Lys Pro Arg Arg Asn Leu Glu Glu Asp Asp Tyr Leu His Lys Asp Thr
20 25 30

Gly Glu Thr Ser Met Leu Lys Arg Pro Val Leu Leu His Leu His Gln
35 40 45

Thr Ala His Ala Asp Glu Phe Asp Cys Pro Ser Glu Leu Gln His Thr
50 55 60

Gln Glu Leu Phe Pro Gln Trp His Leu Pro Ile Lys Ile Ala Ala Ile
65 70 75 80

Ile Ala Ser Leu Thr Phe Leu Tyr Thr Leu Leu Arg Glu Val Ile His
85 90 95

Pro Leu Ala Thr Ser His Gln Gln Tyr Phe Tyr Lys Ile Pro Ile Leu
100 105 110

Val Ile Asn Lys Val Leu Pro Met Val Ser Ile Thr Leu Leu Ala Leu
115 120 125

Val Tyr Leu Pro Gly Val Ile Ala Ala Ile Val Gln Leu His Asn Gly
130 135 140

Thr Lys Tyr Lys Lys Phe Pro His Trp Leu Asp Lys Trp Met Leu Thr
145 150 155 160

Arg Lys Gln Phe Gly Leu Leu Ser Phe Phe Phe Ala Val Leu His Ala
165 170 175

Ile Tyr Ser Leu Ser Tyr Pro Met Arg Arg Ser Tyr Arg Tyr Lys Leu
180 185 190

Leu Asn Trp Ala Tyr Gln Gln Val Gln Gln Asn Lys Glu Asp Ala Trp
195 200 205

Ile Glu His Asp Val Trp Arg Met Glu Ile Tyr Val Ser Leu Gly Ile
210 215 220

Val Gly Leu Ala Ile Leu Ala Leu Leu Ala Val Thr Ser Ile Pro Ser
225 230 235 240

Val Ser Asp Ser Leu Thr Trp Arg Glu Phe His Tyr Ile Gln Ser Lys
245 250 255

Leu Gly Ile Val Ser Leu Leu Leu Gly Thr Ile His Ala Leu Ile Phe
260 265 270

Ala Trp Asn Lys Trp Ile Asp Ile Lys Gln Phe Val Trp Tyr Thr Pro
275 280 285

Pro Thr Phe Met Ile Ala Val Phe Leu Pro Ile Val Val Leu Ile Phe
290 295 300

Lys Ser Ile Leu Phe Leu Pro Cys Leu Arg Lys Lys Ile Leu Lys Ile
305 310 315 320

Arg His Gly Trp Glu Asp Val Thr Lys Ile Asn Lys Thr Glu Ile Cys

325 330 335

Ser Gln Leu

<210> 737
<211> 2172
<212> DNA
<213> Homo sapiens

<400> 737
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aaaatattgg aattttattc atcttaaaaa ttggacccgg ccttatttac catctttaat 120
ccattttagt actatgggtg agtacatgga attgaagtct ggcttaaatc ttcagaaagt 180
tatatatcta ttttatttta ttttttgag acagagtctc gctgtgtcac ccaggctgga 240
gtgcggtgcc acaatcttgg ctcactgcaa cctctgagtc ccaggttcaa gcgatactca 300
tgcctcggcc tcctgagtag ctgggactac aggcgtgcac caccacatct ggctaatctt 360
tttttgtatt tttagtagag acggggtttc actgtggtct ccatctcctg acctcgtgat 420
ccgcctgcct cccaaagtgc tgggattaca ggcatgagcc accgcacaca gctgggactg 480
ggtaatttat aaagaaaaga ggtttaatga ctcacagttc cgcatggctg gagaggcctc 540
aggaaactta caatcatggt ggaaggcgaa ggggaagcaa ggcacgtctt acatggtggc 600
aggagagaac gagtgagggg ggagactgcc acaaactttt tttttttgag acaagagtct 660
ggccctgttg cccaggctgg agtgcagtgg catgatctca gctcactgca acctctgcct 720
cacaggttca agcaattctc atgcctcagc ctcccgcata gctgggacca caggtatgca 780
ccaccacacc tagctaattt ttgtagtttt agtagagatg gggtctcact atgttgctca 840
ggctggtcta aaactcctgg gctccagcaa tccgcctgcc ttggcctccc aaagtgctgg 900
ggttacaggc ataagccacc acatccagcc tgccacatac ttttaaacta tcaggtctca 960
tgagaactca tgcactatca caagaatagc atggggaaaa tcccccccat aatccaatca 1020
cctcccacca ggtctcctcc gacacgtggg attgggtggg gacacagagc caaaccgtat 1080
cagatgctgc aggggctggg gacactgaga ccactcagac ctggtgtctc tgtcactctt 1140
ctgggctctg tctgtctcca ggacctccct ccccttccat ggtatagaag gaaagtgctg 1200
taaggtgcaa attgcacagg aactccttaa gacatacatc atccactcag cagttttagg 1260
ttcgcagcaa aatggagtgg aaggaacaga aatttcctgt gcacccctcc ccgctgtctc 1320
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<211> 2455
<212> DNA
<213> Homo sapiens

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<211> 2455
<212> DNA
<213> Homo sapiens

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<210> 740
<211> 62
<212> PRT
<213> Homo sapiens

<400> 740
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His Gly Gly Arg Arg Arg Gly Ser Lys Ala Arg Leu Thr Trp Trp Gln
20 25 30

Glu Arg Thr Ser Glu Gly Gly Asp Cys His Lys Leu Phe Phe Phe Glu
35 40 45

Thr Arg Val Trp Pro Cys Cys Pro Gly Trp Ser Ala Val Ala
50 55 60

<210> 741
<211> 135
<212> PRT
<213> Homo sapiens

<400> 741
Met Val Glu Gly Glu Gly Glu Ala Arg His Val Leu His Gly Gly Arg
5 10 15

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            20                  25                  30

Gln Glu Ser Gly Pro Val Ala Gln Ala Gly Val Gln Trp His Asp Leu
        35                  40                  45

Ser Ser Leu Gln Pro Leu Pro His Arg Phe Lys Gln Phe Ser Cys Leu
    50                  55                  60

Ser Leu Pro His Ser Trp Asp His Arg Tyr Ala Pro Pro His Leu Ala
65                  70                  75                  80

Asn Phe Cys Ser Phe Ser Arg Asp Gly Val Ser Leu Cys Cys Ser Gly
                85                  90                  95

Trp Ser Lys Thr Pro Gly Leu Gln Gln Ser Ala Cys Leu Gly Leu Pro
            100                 105                 110

Lys Cys Trp Gly Tyr Arg His Lys Pro Pro His Pro Ala Cys His Ile
        115                 120                 125

Leu Leu Asn Tyr Gln Val Ser
    130                 135
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<210> 742
<211> 77
<212> PRT
<213> Homo sapiens

<400> 742

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Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro Ile Ile Gln
                5                   10                  15

Ser Pro Pro Thr Arg Ser Pro Pro Thr Arg Gly Ile Gly Trp Gly His
            20                  25                  30

Arg Ala Lys Pro Tyr Gln Met Leu Gln Gly Leu Gly Thr Leu Arg Pro
        35                  40                  45

Leu Arg Pro Gly Val Ser Val Thr Leu Leu Gly Ser Val Cys Leu Gln
    50                  55                  60

Asp Leu Pro Pro Leu Pro Trp Tyr Arg Arg Lys Val Leu
65                  70                  75
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<210> 743
<211> 60
<212> PRT
<213> Homo sapiens

<400> 743

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Met Leu Val His Ile Tyr Ser Cys Cys Gly Met Val Tyr Arg Phe Gly
                5                   10                  15

Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu Ala Ser Leu Gly Ser Ser
            20                  25                  30
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Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp Arg Gln Ala Asp Pro Ser
35 40 45

Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe
50 55 60

<210> 744
<211> 76
<212> PRT
<213> Homo sapiens

<400> 744
Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys
5 10 15

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg
20 25 30

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro
35 40 45
Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly
50 55 60

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys
65 70 75

<210> 745
<211> 76
<212> PRT
<213> Homo sapiens

<400> 745
Met Val Lys Ser Arg Phe Thr Lys Asn Thr Lys Ile Thr Gln Ala Trp
5 10 15

Trp Arg Ala Pro Val Ile Pro Gly Thr Arg Glu Ala Glu Gly Gly Glu
20 25 30

Ser Leu Glu Pro Gly Arg Leu Arg Glu Glu Asn Arg Leu Asn Pro Gly
35 40 45

Gly Arg Gly Cys Ser Glu Pro Arg Ser Cys Cys Cys Thr Pro Ala Trp
50 55 60

Ser Thr Glu Gln Asp Ser Ala Ser Lys Thr Asn Lys
65 70 75

<210> 746
<211> 80
<212> PRT
<213> Homo sapiens

<400> 746
Met Leu Leu His Ser Ser Leu Val Asn Arg Ala Arg Leu Cys Leu Lys

5 10 15

Asn Lys Gln Ile Asn Lys Gln Thr Asn Lys Thr Glu Arg Phe Cys Cys
20 25 30

Asn Val Gln Gly Ala Ile Cys Ser Phe Lys Lys Ile Ile Phe Gly Gln
35 40 45

Ala Gln Trp Leu Thr Pro Val Ile Pro Ala Leu Trp Glu Ala Lys Val
50 55 60

Gly Gly Ser Phe Glu Val Arg Ser Leu Arg Ser Ala Trp Pro Thr Trp
65 70 75 80

<210> 747
<211> 72
<212> PRT
<213> Homo sapiens

<400> 747
Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro His Asn Pro
5 10 15

Ile Thr Ser His Gln Val Ser Ser Asp Thr Trp Asp Trp Val Gly Thr
20 25 30

Gln Ser Gln Thr Val Ser Asp Ala Ala Gly Ala Gly Asp Thr Glu Thr
35 40 45

Thr Gln Thr Trp Cys Leu Cys His Ser Ser Gly Leu Cys Leu Ser Pro
50 55 60

Gly Pro Pro Ser Pro Ser Met Val
65 70

<210> 748
<211> 77
<212> PRT
<213> Homo sapiens

<400> 748
Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro Ile Ile Gln
5 10 15

Ser Pro Pro Thr Arg Ser Pro Pro Thr Arg Gly Ile Gly Trp Gly His
20 25 30

Arg Ala Lys Pro Tyr Gln Met Leu Gln Gly Leu Gly Thr Leu Arg Pro
35 40 45

Leu Arg Pro Gly Val Ser Val Thr Leu Leu Gly Ser Val Cys Leu Gln
50 55 60

Asp Leu Pro Pro Leu Pro Trp Tyr Arg Arg Lys Val Leu
65 70 75

<210> 749
<211> 60
<212> PRT
<213> Homo sapiens

<400> 749
Met Leu Val His Ile Tyr Ser Cys Cys Gly Met Val Tyr Arg Phe Gly
5 10 15

Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu Ala Ser Leu Gly Ser Ser
20 25 30

Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp Arg Gln Ala Asp Pro Ser
35 40 45

Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe
50 55 60

<210> 750
<211> 76
<212> PRT
<213> Homo sapiens

<400> 750
Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys
5 10 15

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg
20 25 30

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro
35 40 45

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly
50 55 60

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys
65 70 75

<210> 751
<211> 2479
<212> DNA
<213> Homo sapiens

<400> 751
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<210> 752
<211> 492
<212> PRT
<213> Homo sapiens

<400> 752
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Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val
20 25 30

Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro
35 40 45

Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
50 55 60

Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
65 70 75 80

Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
85 90 95

Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys

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            100                 105                 110

Cys Ser Asn Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn
        115                 120                 125

Pro Ser Asn Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp
    130                 135                 140

Glu Asn Arg Cys Val Arg Leu Tyr Gly Pro Asn Phe Ile Leu Gln Met
145                 150                 155                 160

Tyr Ser Ser Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp
                165                 170                 175

Asn Glu Asn Tyr Gly Arg Ala Ala Cys Arg Asp Met Gly Tyr Lys Asn
            180                 185                 190

Asn Phe Tyr Ser Ser Gln Gly Ile Val Asp Asp Ser Gly Ser Thr Ser
        195                 200                 205

Phe Met Lys Leu Asn Thr Ser Ala Gly Asn Val Asp Ile Tyr Lys Lys
    210                 215                 220

Leu Tyr His Ser Asp Ala Cys Ser Ser Lys Ala Val Val Ser Leu Arg
225                 230                 235                 240

Cys Leu Ala Cys Gly Val Asn Leu Asn Ser Ser Arg Gln Ser Arg Ile
                245                 250                 255

Val Gly Gly Glu Ser Ala Leu Pro Gly Ala Trp Pro Trp Gln Val Ser
            260                 265                 270

Leu His Val Gln Asn Val His Val Cys Gly Gly Ser Ile Ile Thr Pro
        275                 280                 285

Glu Trp Ile Val Thr Ala Ala His Cys Val Glu Lys Pro Leu Asn Asn
    290                 295                 300

Pro Trp His Trp Thr Ala Phe Ala Gly Ile Leu Arg Gln Ser Phe Met
305                 310                 315                 320

Phe Tyr Gly Ala Gly Tyr Gln Val Gln Lys Val Ile Ser His Pro Asn
                325                 330                 335

Tyr Asp Ser Lys Thr Lys Asn Asn Asp Ile Ala Leu Met Lys Leu Gln
            340                 345                 350

Lys Pro Leu Thr Phe Asn Asp Leu Val Lys Pro Val Cys Leu Pro Asn
        355                 360                 365

Pro Gly Met Met Leu Gln Pro Glu Gln Leu Cys Trp Ile Ser Gly Trp
    370                 375                 380

Gly Ala Thr Glu Glu Lys Gly Lys Thr Ser Glu Val Leu Asn Ala Ala
385                 390                 395                 400

Lys Val Leu Leu Ile Glu Thr Gln Arg Cys Asn Ser Arg Tyr Val Tyr
                405                 410                 415
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Asp Asn Leu Ile Thr Pro Ala Met Ile Cys Ala Gly Phe Leu Gln Gly
            420                 425                 430

Asn Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Thr Ser
        435                 440                 445

Asn Asn Asn Ile Trp Trp Leu Ile Gly Asp Thr Ser Trp Gly Ser Gly
    450                 455                 460

Cys Ala Lys Ala Tyr Arg Pro Gly Val Tyr Gly Asn Val Met Val Phe
465                 470                 475                 480

Thr Asp Trp Ile Tyr Arg Gln Met Lys Ala Asn Gly
                485                 490
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<210> 753
<211> 683
<212> DNA
<213> Homo sapiens

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agaaagcact gtgcatcacc ttgaccctgg ggaccttcct cgtgggagct gcgctggccg 360
ctggcctact ctggaagttc atgggcagca agtgctccaa ctctgggata gagtgcgact 420
cctcaggtac ctgcatcaac ccctctaact ggtgtgatgg cgtgtcacac tgccccggcg 480
gggaggacga gaatcggtgt gttcgcctct acggaccaaa cttcatcctt cagatgtact 540
catctcagag gaagtcctgg caccctgtgt gccaagacga ctggaacgag aactacgggc 600
gggcggcctg cagggacatg ggctataaga ataattttta ctctagccaa ggaatagtgg 660
atgacagcgg atccaccagc ttt                                         683
```

```
<210> 754
<211> 209
<212> PRT
<213> Homo sapiens

<400> 754
Met Ala Leu Asn Ser Gly Ser Pro Pro Ala Ile Gly Pro Tyr Tyr Glu
 1               5                  10                  15
Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val
            20                  25                  30
Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro
        35                  40                  45
Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
    50                  55                  60
Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
65                  70                  75                  80
Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
                85                  90                  95
```

```
Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys
            100                 105                 110
Cys Ser Asn Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn
        115                 120                 125
Pro Ser Asn Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp
    130                 135                 140
Glu Asn Arg Cys Val Arg Leu Tyr Gly Pro Asn Phe Ile Leu Gln Met
145                 150                 155                 160
Tyr Ser Ser Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp
                165                 170                 175
Asn Glu Asn Tyr Gly Arg Ala Ala Cys Arg Asp Met Gly Tyr Lys Asn
            180                 185                 190
Asn Phe Tyr Ser Ser Gln Gly Ile Val Asp Asp Ser Gly Ser Thr Ser
        195                 200                 205
Phe


<210> 755
<211> 27
<212> PRT
<213> Homo sapiens

<400> 755
Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr
 1               5                  10                  15
Glu Ala Arg Arg His Tyr Asp Glu Gly Val Arg
            20                  25


<210> 756
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 756
ggatccgccg ccaccatgtc actttctagc ctgct                                 35

<210> 757
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 757
gtcgactcag ctggaccaca gccgcag                                          27

<210> 758
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer
```

<400> 758
ggatccgccg ccaccatggg ctgcaggctg ctct 34

<210> 759
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 759
gtcgactcag aaatcctttc tcttgac 27

<210> 760
<211> 936
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...()
<223> n = A,T,C or G

<400> 760
atgggctgca ggctgntctg ctgtgcggtt ctctgtctcc tgggagcggt ccccatggaa 60
acgggagtta cgcagacacc aagacacctg gtcatgggaa tgacaaataa gaagtctttg 120
aaatgtgaac aacatctggg tcataacgct atgtattggt acaagcaaag tgctaagaag 180
ccactggagc tcatgtttgt ctacagtctt gaagaacggg ttgaaaacaa cagtgtgcca 240
agtcgcttct cacctgaatg ccccaacagc tctcacttat tccttcacct acacaccctg 300
cagccagaag actcggccct gtatctctgc gccagcagcc aagaccggac aagcagctcc 360
tacgagcagt acttcgggcc gggcaccagg ctcacggtca cagaggacct gaaaaacgtg 420
ttcccacccg aggtcgctgt gtttgagcca tcagaagcag agatctccca cacccaaaag 480
gccacactgg tgtgcctggc cacaggcttc taccccgacc acgtggagct gagctggtgg 540
gtgaatggga aggaggtgca cagtggggtc agcacagacc cgcagcccct caaggagcag 600
cccgccctca atgactccag atactgcctg agcagccgcc tgagggtctc ggccaccttc 660
tggcagaacc cccgcaacca cttccgctgt caagtccagt tctacgggct ctcggagaat 720
gacgagtgga cccaggatag ggccaaacct gtcacccaga tcgtcagcgc cgaggcctgg 780
ggtagagcag actgtggctt cacctccgag tcttaccagc aaggggtcct gtctgccacc 840
atcctctatg agatcttgct agggaaggcc accttgtatg ccgtgctggt cagtgccctc 900
gtgctgatgg ccatggtcaa gagaaaggat ttctga 936

<210> 761
<211> 834
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...()
<223> n = A,T,C or G

<400> 761
atgtcacttt ctagcctgct naaggtggtc acagcttcac tgtggctagg acctggcatt 60
gcccagaaga taactcaaac ccaaccagga atgttcgtgc aggaaaagga ggctgtgact 120
ctggactgca catatgacac cagtgatcaa agttatggtc tcttctggta caagcagccc 180

agcagtgggg aaatgatttt tcttatttat caggggtctt atgacgagca aaatgcaaca 240
gaaggtcgct actcattgaa tttccagaag gcaagaaaat ccgccaacct tgtcatctcc 300
gcttcacaac tgggggactc agcaatgtat ttctgtgcaa tgagagaggg cgcgggagga 360
ggaaacaaac tcacctttgg gacaggcact cagctaaaag tggaactcaa tatccagaac 420
cctgaccctg ccgtgtacca gctgagagac tctaaatcca gtgacaagtc tgtctgccta 480
ttcaccgatt ttgattctca aacaaatgtg tcacaaagta aggattctga tgtgtatatc 540
acagacaaaa ctgtgctaga catgaggtct atggacttca agagcaacag tgctgtggcc 600
tggagcaaca aatctgactt tgcatgtgca aacgccttca acaacagcat tattccagaa 660
gacaccttct tccccagccc agaaagttcc tgtgatgtca agctggtcga gaaaagcttt 720
gaaacagata cgaacctaaa ctttcaaaac ctgtcagtga ttgggttccg aatcctcctc 780
ctgaaagtgg ccgggtttaa tctgctcatg acgctgcggc tgtggtccag ctga 834

<210> 762
<211> 311
<212> PRT
<213> Homo sapiens

<220>
<221> variant
<222> (1)...(311)
<223> Xaa = Any amino acid

<400> 762
Met Gly Cys Arg Leu Xaa Cys Cys Ala Val Leu Cys Leu Leu Gly Ala
5 10 15

Val Pro Met Glu Thr Gly Val Thr Gln Thr Pro Arg His Leu Val Met
20 25 30

Gly Met Thr Asn Lys Lys Ser Leu Lys Cys Glu Gln His Leu Gly His
35 40 45

Asn Ala Met Tyr Trp Tyr Lys Gln Ser Ala Lys Lys Pro Leu Glu Leu
50 55 60

Met Phe Val Tyr Ser Leu Glu Glu Arg Val Glu Asn Asn Ser Val Pro
65 70 75 80

Ser Arg Phe Ser Pro Glu Cys Pro Asn Ser Ser His Leu Phe Leu His
85 90 95

Leu His Thr Leu Gln Pro Glu Asp Ser Ala Leu Tyr Leu Cys Ala Ser
100 105 110

Ser Gln Asp Arg Thr Ser Ser Ser Tyr Glu Gln Tyr Phe Gly Pro Gly
115 120 125

Thr Arg Leu Thr Val Thr Glu Asp Leu Lys Asn Val Phe Pro Pro Glu
130 135 140

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys
145 150 155 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu
165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
180 185 190

```
Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
        195                 200                 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
    210                 215                 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225                 230                 235                 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
                245                 250                 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr
            260                 265                 270

Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
        275                 280                 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
    290                 295                 300

Met Val Lys Arg Lys Asp Phe
305                 310


<210> 763
<211> 277
<212> PRT
<213> Homo sapiens

<400> 763
Met Ser Leu Ser Ser Leu Leu Lys Val Val Thr Ala Ser Leu Trp Leu
                5                   10                  15

Gly Pro Gly Ile Ala Gln Lys Ile Thr Gln Thr Gln Pro Gly Met Phe
            20                  25                  30

Val Gln Glu Lys Glu Ala Val Thr Leu Asp Cys Thr Tyr Asp Thr Ser
        35                  40                  45

Asp Gln Ser Tyr Gly Leu Phe Trp Tyr Lys Gln Pro Ser Ser Gly Glu
    50                  55                  60

Met Ile Phe Leu Ile Tyr Gln Gly Ser Tyr Asp Glu Gln Asn Ala Thr
65                  70                  75                  80

Glu Gly Arg Tyr Ser Leu Asn Phe Gln Lys Ala Arg Lys Ser Ala Asn
                85                  90                  95

Leu Val Ile Ser Ala Ser Gln Leu Gly Asp Ser Ala Met Tyr Phe Cys
            100                 105                 110

Ala Met Arg Glu Gly Ala Gly Gly Gly Asn Lys Leu Thr Phe Gly Thr
        115                 120                 125

Gly Thr Gln Leu Lys Val Glu Leu Asn Ile Gln Asn Pro Asp Pro Ala
    130                 135                 140
```

Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu
145 150 155 160

Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser
165 170 175

Asp Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp
180 185 190

Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala
195 200 205

Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe
210 215 220

Pro Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe
225 230 235 240

Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe
245 250 255

Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu
260 265 270

Arg Leu Trp Ser Ser
275

<210> 764
<211> 1536
<212> DNA
<213> Homo sapiens

<400> 764
atgtacaacc tgttgctgtc ctacgacaga catggggacc acctgcagcc cctggacctc 60
gtgcccaatc accagggtct caccccttc aagctggctg gagtggaggg taacactgtg 120
atgtttcagc acctgatgca gaagcggaag cacacccagt ggacgtatgg accactgacc 180
tcgactctct atgacctcac agagatcgac tcctcagggg atgagcagtc cctgctggaa 240
cttatcatca ccaccaagaa gcgggaggct cgccagatcc tggaccagac gccggtgaag 300
gagctggtga gcctcaagtg gaagcggtac gggcggccgt acttctgcat gctgggtgcc 360
atatatctgc tgtacatcat ctgcttcacc atgtgctgca tctaccgccc cctcaagccc 420
aggaccaata accgcacgag cccccgggac aacaccctct tacagcagaa gctacttcag 480
gaagcctaca tgaccctaa ggacgatatc cggctggtcg gggagctggt gactgtcatt 540
ggggctatca tcatcctgct ggtagaggtt ccagacatct tcagaatggg ggtcactcgc 600
ttctttggac agaccatcct tgggggccca ttccatgtcc tcatcatcac ctatgccttc 660
atggtgctgg tgaccatggt gatgcggctc atcagtgcca gcggggaggt ggtacccatg 720
tcctttgcac tcgtgctggg ctggtgcaac gtcatgtact tcgcccgagg attccagatg 780
ctaggcccct tcaccatcat gattcagaag atgatttttg gcgacctgat gcgattctgc 840
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gaggaccccg aggagctagg ccacttctac gactacccca tggccctgtt cagcaccttc 960
gagctgttcc ttaccatcat cgatggccca gccaactaca acgtggacct gcccttcatg 1020
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attgccatga tgggcgacac tcactggcga gtggcccatg agcgggatga gctgtggagg 1140
gcccagattg tggccaccac ggtgatgctg gagcggaagc tgcctcgctg cctgtggcct 1200
cgctccggga tctgcggacg ggagtatggc ctgggagacc gctggttcct gcgggtggaa 1260
gacaggcaag atctcaaccg gcagcggatc caacgctacg cacaggcctt ccacacccgg 1320
ggctctgagg atttggacaa agactcagtg gaaaaactag agctgggctg tcccttcagc 1380

ccccacctgt cccttcctat gccctcagtg tctcgaagta cctcccgcag cagtgccaat 1440
tgggaaaggc ttcggcaagg gaccctgagg agagacctgc gtgggataat caacaggggt 1500
ctggaggacg gggagagctg ggaatatcag atctga 1536

<210> 765
<211> 1533
<212> DNA
<213> Homo sapiens

<400> 765
atgtacaacc tgttgctgtc ctacgacaga catggggacc acctgcagcc cctggacctc 60
gtgcccaatc accagggtct cacccctttc aagctggctg gagtggaggg taacactgtg 120
atgtttcagc acctgatgca gaagcggaag cacacccagt ggacgtatgg accactgacc 180
tcgactctct atgacctcac agagatcgac tcctcagggg atgagcagtc cctgctggaa 240
cttatcatca ccaccaagaa gcgggaggct cgccagatcc tggaccagac gccggtgaag 300
gagctggtga gcctcaagtg gaagcggtac gggcggccgt acttctgcat gctgggtgcc 360
atatatctgc tgtacatcat ctgcttcacc atgtgctgca tctaccgccc cctcaagccc 420
aggaccaata accgcacgag cccccgggac aacaccctct tacagcagaa gctacttcag 480
gaagcctaca tgacccctaa ggacgatatc cggctggtcg gggagctggt gactgtcatt 540
ggggctatca tcatcctgct ggtagaggtt ccagacatct tcagaatggg ggtcactcgc 600
ttctttggac agaccatcct tggggggcca ttccatgtcc tcatcatcac ctatgccttc 660
atggtgctgg tgaccatggt gatgcggctc atcagtgcca gcggggaggt ggtacccatg 720
tcctttgcac tcgtgctggg ctggtgcaac gtcatgtact tcgcccgagg attccagatg 780
ctaggcccct tcaccatcat gattcagaag atgatttttg gcgacctgat gcgattctgc 840
tggctgatgg ctgtggtcat cctgggcttt gcttcagcct tctatatcat cttccagaca 900
gaggaccccg aggagctagg ccacttctac gactacccca tggccctgtt cagcaccttc 960
gagctgttcc ttaccatcat cgatggccca gccaactaca acgtggacct gcccttcatg 1020
tacagcatca cctatgctgc ctttgccatc atcgccacac tgctcatgct caacctcctc 1080
attgccatga tgggcgacac tcactggcga gtggcccatg agcgggatga gctgtggagg 1140
gcccagattg tggccaccac ggtgatgctg gagcggaagc tgcctcgctg cctgtggcct 1200
cgctccggga tctgcggacg ggagtatggc ctgggagacc gctggttcct gcgggtggaa 1260
gacaggcaag atctcaaccg gcagcggatc caacgctacg cacaggcctt ccacacccgg 1320
ggctctgagg atttggacaa agactcagtg gaaaaactag agctgggctg tcccttcagc 1380
ccccacctgt cccttcctat gccctcagtg tctcgaagta cctcccgcag cagtgccaat 1440
tgggaaaggc ttcggcaagg gaccctgagg agagacctgc gtgggataat caacaggggt 1500
ctggaggacg gggagagctg ggaatatcag atc 1533

<210> 766
<211> 511
<212> PRT
<213> Homo sapiens

<400> 766
Met Tyr Asn Leu Leu Leu Ser Tyr Asp Arg His Gly Asp His Leu Gln
5 10 15

Pro Leu Asp Leu Val Pro Asn His Gln Gly Leu Thr Pro Phe Lys Leu
20 25 30

Ala Gly Val Glu Gly Asn Thr Val Met Phe Gln His Leu Met Gln Lys
35 40 45

Arg Lys His Thr Gln Trp Thr Tyr Gly Pro Leu Thr Ser Thr Leu Tyr
50 55 60

Asp Leu Thr Glu Ile Asp Ser Ser Gly Asp Glu Gln Ser Leu Leu Glu
65 70 75 80

```
Leu Ile Ile Thr Thr Lys Lys Arg Glu Ala Arg Gln Ile Leu Asp Gln
                85                  90                  95

Thr Pro Val Lys Glu Leu Val Ser Leu Lys Trp Lys Arg Tyr Gly Arg
            100                 105                 110

Pro Tyr Phe Cys Met Leu Gly Ala Ile Tyr Leu Leu Tyr Ile Ile Cys
        115                 120                 125

Phe Thr Met Cys Cys Ile Tyr Arg Pro Leu Lys Pro Arg Thr Asn Asn
    130                 135                 140

Arg Thr Ser Pro Arg Asp Asn Thr Leu Leu Gln Gln Lys Leu Leu Gln
145                 150                 155                 160

Glu Ala Tyr Met Thr Pro Lys Asp Asp Ile Arg Leu Val Gly Glu Leu
                165                 170                 175

Val Thr Val Ile Gly Ala Ile Ile Ile Leu Leu Val Glu Val Pro Asp
            180                 185                 190

Ile Phe Arg Met Gly Val Thr Arg Phe Phe Gly Gln Thr Ile Leu Gly
        195                 200                 205

Gly Pro Phe His Val Leu Ile Ile Thr Tyr Ala Phe Met Val Leu Val
    210                 215                 220

Thr Met Val Met Arg Leu Ile Ser Ala Ser Gly Glu Val Val Pro Met
225                 230                 235                 240

Ser Phe Ala Leu Val Leu Gly Trp Cys Asn Val Met Tyr Phe Ala Arg
                245                 250                 255

Gly Phe Gln Met Leu Gly Pro Phe Thr Ile Met Ile Gln Lys Met Ile
            260                 265                 270

Phe Gly Asp Leu Met Arg Phe Cys Trp Leu Met Ala Val Val Ile Leu
        275                 280                 285

Gly Phe Ala Ser Ala Phe Tyr Ile Ile Phe Gln Thr Glu Asp Pro Glu
    290                 295                 300

Glu Leu Gly His Phe Tyr Asp Tyr Pro Met Ala Leu Phe Ser Thr Phe
305                 310                 315                 320

Glu Leu Phe Leu Thr Ile Ile Asp Gly Pro Ala Asn Tyr Asn Val Asp
                325                 330                 335

Leu Pro Phe Met Tyr Ser Ile Thr Tyr Ala Ala Phe Ala Ile Ile Ala
            340                 345                 350

Thr Leu Leu Met Leu Asn Leu Leu Ile Ala Met Met Gly Asp Thr His
        355                 360                 365

Trp Arg Val Ala His Glu Arg Asp Glu Leu Trp Arg Ala Gln Ile Val
    370                 375                 380

Ala Thr Thr Val Met Leu Glu Arg Lys Leu Pro Arg Cys Leu Trp Pro
```

385 390 395 400

Arg Ser Gly Ile Cys Gly Arg Glu Tyr Gly Leu Gly Asp Arg Trp Phe
405 410 415

Leu Arg Val Glu Asp Arg Gln Asp Leu Asn Arg Gln Arg Ile Gln Arg
420 425 430

Tyr Ala Gln Ala Phe His Thr Arg Gly Ser Glu Asp Leu Asp Lys Asp
435 440 445

Ser Val Glu Lys Leu Glu Leu Gly Cys Pro Phe Ser Pro His Leu Ser
450 455 460

Leu Pro Met Pro Ser Val Ser Arg Ser Thr Ser Arg Ser Ser Ala Asn
465 470 475 480

Trp Glu Arg Leu Arg Gln Gly Thr Leu Arg Arg Asp Leu Arg Gly Ile
485 490 495

Ile Asn Arg Gly Leu Glu Asp Gly Glu Ser Trp Glu Tyr Gln Ile
500 505 510

<210> 767
<211> 134
<212> PRT
<213> Homo sapiens

<400> 767
Met Tyr Asn Leu Leu Leu Ser Tyr Asp Arg His Gly Asp His Leu Gln
5 10 15

Pro Leu Asp Leu Val Pro Asn His Gln Gly Leu Thr Pro Phe Lys Leu
20 25 30

Ala Gly Val Glu Gly Asn Thr Val Met Phe Gln His Leu Met Gln Lys
35 40 45

Arg Lys His Thr Gln Trp Thr Tyr Gly Pro Leu Thr Ser Thr Leu Tyr
50 55 60

Asp Leu Thr Glu Ile Asp Ser Ser Gly Asp Glu Gln Ser Leu Leu Glu
65 70 75 80

Leu Ile Ile Thr Thr Lys Lys Arg Glu Ala Arg Gln Ile Leu Asp Gln
85 90 95

Thr Pro Val Lys Glu Leu Val Ser Leu Lys Trp Lys Arg Tyr Gly Arg
100 105 110

Pro Tyr Phe Cys Met Leu Gly Ala Ile Tyr Leu Leu Tyr Ile Ile Cys
115 120 125

Phe Thr Met Cys Cys Ile
130

<210> 768
<211> 55
<212> PRT
<213> Homo sapiens

<400> 768
Ala Tyr Arg Pro Leu Lys Pro Arg Thr Asn Asn Arg Thr Ser Pro Arg
5 10 15

Asp Asn Thr Leu Leu Gln Gln Lys Leu Leu Gln Glu Ala Tyr Met Thr
20 25 30

Pro Lys Asp Asp Ile Arg Leu Val Gly Glu Leu Val Thr Val Ile Gly
35 40 45

Ala Ile Ile Ile Leu Leu Val
50 55

<210> 769
<211> 39
<212> PRT
<213> Homo sapiens

<400> 769
Glu Val Pro Asp Ile Phe Arg Met Gly Val Thr Arg Phe Phe Gly Gln
5 10 15

Thr Ile Leu Gly Gly Pro Phe His Val Leu Ile Ile Thr Tyr Ala Phe
20 25 30

Met Val Leu Val Thr Met Val
35

<210> 770
<211> 19
<212> PRT
<213> Homo sapiens

<400> 770
Met Arg Leu Ile Ser Ala Ser Gly Glu Val Val Pro Met Ser Phe Ala
5 10 15

Leu Val Leu

<210> 771
<211> 52
<212> PRT
<213> Homo sapiens

<400> 771
Gly Trp Cys Asn Val Met Tyr Phe Ala Arg Gly Phe Gln Met Leu Gly
5 10 15

Pro Phe Thr Ile Met Ile Gln Lys Met Ile Phe Gly Asp Leu Met Arg

20 25 30

Phe Cys Trp Leu Met Ala Val Val Ile Leu Gly Phe Ala Ser Ala Phe
35 40 45

Tyr Ile Ile Phe
50

<210> 772
<211> 213
<212> PRT
<213> Homo sapiens

<400> 772
Gln Thr Glu Asp Pro Glu Glu Leu Gly His Phe Tyr Asp Tyr Pro Met
5 10 15

Ala Leu Phe Ser Thr Phe Glu Leu Phe Leu Thr Ile Ile Asp Gly Pro
20 25 30

Ala Asn Tyr Asn Val Asp Leu Pro Phe Met Tyr Ser Ile Thr Tyr Ala
35 40 45

Ala Phe Ala Ile Ile Ala Thr Leu Leu Met Leu Asn Leu Leu Ile Ala
50 55 60

Met Met Gly Asp Thr His Trp Arg Val Ala His Glu Arg Asp Glu Leu
65 70 75 80

Trp Arg Ala Gln Ile Val Ala Thr Thr Val Met Leu Glu Arg Lys Leu
85 90 95

Pro Arg Cys Leu Trp Pro Arg Ser Gly Ile Cys Gly Arg Glu Tyr Gly
100 105 110

Leu Gly Asp Arg Trp Phe Leu Arg Val Glu Asp Arg Gln Asp Leu Asn
115 120 125

Arg Gln Arg Ile Gln Arg Tyr Ala Gln Ala Phe His Thr Arg Gly Ser
130 135 140

Glu Asp Leu Asp Lys Asp Ser Val Glu Lys Leu Glu Leu Gly Cys Pro
145 150 155 160

Phe Ser Pro His Leu Ser Leu Pro Met Pro Ser Val Ser Arg Ser Thr
165 170 175

Ser Arg Ser Ser Ala Asn Trp Glu Arg Leu Arg Gln Gly Thr Leu Arg
180 185 190

Arg Asp Leu Arg Gly Ile Ile Asn Arg Gly Leu Glu Asp Gly Glu Ser
195 200 205

Trp Glu Tyr Gln Ile
210

<210> 773
<211> 1302
<212> DNA
<213> Homo sapiens

<400> 773
tggacaaagg gggtcacaca ttccttccat acggttgagc ctctacctgc ctggtgctgg 60
tcacagttca gcttcttcat gatggtggat cccaatggca atgaatccag tgctacatac 120
ttcatcctaa taggcctccc tggtttagaa gaggctcagt tctggttggc cttcccattg 180
tgctccctct accttattgc tgtgctaggt aacttgacaa tcatctacat tgtgcggact 240
gagcacagcc tgcatgagcc catgtatata tttctttgca tgctttcagg cattgacatc 300
ctcatctcca cctcatccat gcccaaaatg ctggccatct tctggttcaa ttccactacc 360
atccagtttg atgcttgtct gctacagatg tttgccatcc actccttatc tggcatggaa 420
tccacagtgc tgctggccat ggcttttgac cgctatgtgg ccatctgtca cccactgcgc 480
catgccacag tacttacgtt gcctcgtgtc accaaaattg gtgtggctgc tgtggtgcgg 540
ggggctgcac tgatggcacc ccttcctgtc ttcatcaagc agctgccctt ctgccgctcc 600
aatatccttt cccattccta ctgcctacac caagatgtca tgaagctggc ctgtgatgat 660
atccgggtca atgtcgtcta tggccttatc gtcatcatct ccgccattgg cctggactca 720
cttctcatct ccttctcata tctgcttatt cttaagactg tgttgggctt gacacgtgaa 780
gcccaggcca aggcatttgg cacttgcgtc tctcatgtgt gtgctgtgtt catattctat 840
gtacctttca ttggattgtc catggtgcat cgctttagca agcggcgtga ctctccgctg 900
cccgtcatct tggccaatat ctatctgctg gttcctcctg tgctcaaccc aattgtctat 960
ggagtgaaga caaaggagat tcgacagcgc atccttcgac ttttccatgt ggccacacac 1020
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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

<400> 775

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<210> 776
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<212> DNA
<213> Homo sapiens

<400> 776

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<211> 318
<212> PRT
<213> Homo sapiens

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Pro Leu Cys Ser Leu Tyr Leu Ile Ala Val Leu Gly Asn Leu Thr Ile
        35                  40                  45

Ile Tyr Ile Val Arg Thr Glu His Ser Leu His Glu Pro Met Tyr Ile
    50                  55                  60

Phe Leu Cys Met Leu Ser Gly Ile Asp Ile Leu Ile Ser Thr Ser Ser
65                  70                  75                  80

Met Pro Lys Met Leu Ala Ile Phe Trp Phe Asn Ser Thr Thr Ile Gln
                85                  90                  95

Phe Asp Ala Cys Leu Leu Gln Met Phe Ala Ile His Ser Leu Ser Gly
            100                 105                 110

Met Glu Ser Thr Val Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala
        115                 120                 125

Ile Cys His Pro Leu Arg His Ala Thr Val Leu Thr Leu Pro Arg Val
    130                 135                 140

Thr Lys Ile Gly Val Ala Ala Val Val Arg Gly Ala Ala Leu Met Ala
145                 150                 155                 160

Pro Leu Pro Val Phe Ile Lys Gln Leu Pro Phe Cys Arg Ser Asn Ile
                165                 170                 175

Leu Ser His Ser Tyr Cys Leu His Gln Asp Val Met Lys Leu Ala Cys
            180                 185                 190

Asp Asp Ile Arg Val Asn Val Val Tyr Gly Leu Ile Val Ile Ile Ser
        195                 200                 205

Ala Ile Gly Leu Asp Ser Leu Leu Ile Ser Phe Ser Tyr Leu Leu Ile
    210                 215                 220

Leu Lys Thr Val Leu Gly Leu Thr Arg Glu Ala Gln Ala Lys Ala Phe
225                 230                 235                 240

Gly Thr Cys Val Ser His Val Cys Ala Val Phe Ile Phe Tyr Val Pro
                245                 250                 255
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Phe Ile Gly Leu Ser Met Val His Arg Phe Ser Lys Arg Arg Asp Ser
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Pro Leu Pro Val Ile Leu Ala Asn Ile Tyr Leu Leu Val Pro Pro Val
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290 295 300

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<210> 778
<211> 28
<212> PRT
<213> Homo sapiens

<400> 778
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Leu Ile Gly Leu Pro Gly Leu Glu Glu Ala Gln Phe
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<210> 779
<211> 9
<212> PRT
<213> Homo sapiens

<400> 779
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<210> 780
<211> 21
<212> PRT
<213> Homo sapiens

<400> 780
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5 10 15

Ala Cys Leu Leu Gln
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<210> 781
<211> 20
<212> PRT
<213> Homo sapiens

<400> 781
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Thr Leu Pro Arg
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<210> 782
<211> 37
<212> PRT
<213> Homo sapiens

<400> 782
Phe Ile Lys Gln Leu Pro Phe Cys Arg Ser Asn Ile Leu Ser His Ser
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Tyr Cys Leu His Gln Asp Val Met Lys Leu Ala Cys Asp Asp Ile Arg
            20                  25                  30

Val Asn Val Val Tyr
        35


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<211> 13
<212> PRT
<213> Homo sapiens

<400> 783
Lys Thr Val Leu Gly Leu Thr Arg Glu Ala Gln Ala Lys
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<210> 784
<211> 10
<212> PRT
<213> Homo sapiens

<400> 784
Val His Arg Phe Ser Lys Arg Arg Asp Ser
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<210> 785
<211> 22
<212> PRT
<213> Homo sapiens

<400> 785
Lys Thr Lys Glu Ile Arg Gln Arg Ile Leu Arg Leu Phe His Val Ala
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Thr His Ala Ser Glu Pro
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<211> 3245
<212> DNA
<213> Homo sapiens
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<211> 1479
<212> DNA
<213> Homo sapiens

<400> 787
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<211> 1476
<212> DNA
<213> Homo sapiens

<400> 788
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<210> 789
<211> 492
<212> PRT
<213> Homo sapiens

<400> 789
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Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro
35 40 45
Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
50 55 60
Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
65 70 75 80
Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
85 90 95
Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys
100 105 110
Cys Ser Asn Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn
115 120 125
Pro Ser Asn Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp
130 135 140
Glu Asn Arg Cys Val Arg Leu Tyr Gly Ser Asn Phe Ile Leu Gln Val
145 150 155 160
Tyr Ser Ser Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp
165 170 175
Asn Glu Asn Tyr Gly Arg Ala Ala Cys Arg Asp Met Gly Tyr Lys Asn
180 185 190
Asn Phe Tyr Ser Ser Gln Gly Ile Val Asp Asp Ser Gly Ser Thr Ser
195 200 205
Phe Met Lys Leu Asn Thr Ser Ala Gly Asn Val Asp Ile Tyr Lys Lys
210 215 220
Leu Tyr His Ser Asp Ala Cys Ser Ser Lys Ala Val Val Ser Leu Arg
225 230 235 240
Cys Ile Ala Cys Gly Val Asn Leu Asn Ser Ser Arg Gln Ser Arg Ile
245 250 255
Val Gly Gly Glu Ser Ala Leu Pro Gly Ala Trp Pro Trp Gln Val Ser
260 265 270
Leu His Val Gln Asn Val His Val Cys Gly Gly Ser Ile Ile Thr Pro
275 280 285
Glu Trp Ile Val Thr Ala Ala His Cys Val Glu Lys Pro Leu Asn Asn
290 295 300
Pro Trp His Trp Thr Ala Phe Ala Gly Ile Leu Arg Gln Ser Phe Met
305 310 315 320
Phe Tyr Gly Ala Gly Tyr Gln Val Glu Lys Val Ile Ser His Pro Asn
325 330 335
Tyr Asp Ser Lys Thr Lys Asn Asn Asp Ile Ala Leu Met Lys Leu Gln
340 345 350

```
Lys Pro Leu Thr Phe Asn Asp Leu Val Lys Pro Val Cys Leu Pro Asn
        355                 360                 365
Pro Gly Met Met Leu Gln Pro Glu Gln Leu Cys Trp Ile Ser Gly Trp
    370                 375                 380
Gly Ala Thr Glu Glu Lys Gly Lys Thr Ser Glu Val Leu Asn Ala Ala
385                 390                 395                 400
Lys Val Leu Leu Ile Glu Thr Gln Arg Cys Asn Ser Arg Tyr Val Tyr
                405                 410                 415
Asp Asn Leu Ile Thr Pro Ala Met Ile Cys Ala Gly Phe Leu Gln Gly
            420                 425                 430
Asn Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Thr Ser
        435                 440                 445
Lys Asn Asn Ile Trp Trp Leu Ile Gly Asp Thr Ser Trp Gly Ser Gly
    450                 455                 460
Cys Ala Lys Ala Tyr Arg Pro Gly Val Tyr Gly Asn Val Met Val Phe
465                 470                 475                 480
Thr Asp Trp Ile Tyr Arg Gln Met Arg Ala Asp Gly
                485                 490
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<210> 790
<211> 100
<212> PRT
<213> Homo sapiens

<400> 790

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Met Ala Leu Asn Ser Gly Ser Pro Pro Ala Ile Gly Pro Tyr Tyr Glu
                  5                  10                  15
Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val
            20                  25                  30
Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro
        35                  40                  45
Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
    50                  55                  60
Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
 65                  70                  75                  80
Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
                 85                  90                  95
Gly Ala Ala Leu
            100
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<210> 791
<211> 393
<212> PRT
<213> Homo sapiens

<400> 791

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Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys Cys Ser Asn
                  5                  10                  15
Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn Pro Ser Asn
            20                  25                  30
Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp Glu Asn Arg
        35                  40                  45
Cys Val Arg Leu Tyr Gly Ser Asn Phe Ile Leu Gln Val Tyr Ser Ser
    50                  55                  60
Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp Asn Glu Asn
 65                  70                  75                  80
```

Tyr Gly Arg Ala Ala Cys Arg Asp Met Gly Tyr Lys Asn Asn Phe Tyr
85 90 95
Ser Ser Gln Gly Ile Val Asp Asp Ser Gly Ser Thr Ser Phe Met Lys
100 105 110
Leu Asn Thr Ser Ala Gly Asn Val Asp Ile Tyr Lys Lys Leu Tyr His
115 120 125
Ser Asp Ala Cys Ser Ser Lys Ala Val Val Ser Leu Arg Cys Ile Ala
130 135 140
Cys Gly Val Asn Leu Asn Ser Ser Arg Gln Ser Arg Ile Val Gly Gly
145 150 155 160
Glu Ser Ala Leu Pro Gly Ala Trp Pro Trp Gln Val Ser Leu His Val
165 170 175
Gln Asn Val His Val Cys Gly Gly Ser Ile Ile Thr Pro Glu Trp Ile
180 185 190
Val Thr Ala Ala His Cys Val Glu Lys Pro Leu Asn Asn Pro Trp His
195 200 205
Trp Thr Ala Phe Ala Gly Ile Leu Arg Gln Ser Phe Met Phe Tyr Gly
210 215 220
Ala Gly Tyr Gln Val Glu Lys Val Ile Ser His Pro Asn Tyr Asp Ser
225 230 235 240
Lys Thr Lys Asn Asn Asp Ile Ala Leu Met Lys Leu Gln Lys Pro Leu
245 250 255
Thr Phe Asn Asp Leu Val Lys Pro Val Cys Leu Pro Asn Pro Gly Met
260 265 270
Met Leu Gln Pro Glu Gln Leu Cys Trp Ile Ser Gly Trp Gly Ala Thr
275 280 285
Glu Glu Lys Gly Lys Thr Ser Glu Val Leu Asn Ala Ala Lys Val Leu
290 295 300
Leu Ile Glu Thr Gln Arg Cys Asn Ser Arg Tyr Val Tyr Asp Asn Leu
305 310 315 320
Ile Thr Pro Ala Met Ile Cys Ala Gly Phe Leu Gln Gly Asn Val Asp
325 330 335
Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Thr Ser Lys Asn Asn
340 345 350
Ile Trp Trp Leu Ile Gly Asp Thr Ser Trp Gly Ser Gly Cys Ala Lys
355 360 365
Ala Tyr Arg Pro Gly Val Tyr Gly Asn Val Met Val Phe Thr Asp Trp
370 375 380
Ile Tyr Arg Gln Met Arg Ala Asp Gly
385 390

<210> 792
<211> 595
<212> PRT
<213> Homo sapiens

<400> 792
Met Ser Phe Leu Asn Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala
1 5 10 15
Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile
20 25 30
Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp Phe Asp
35 40 45
Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu Phe
50 55 60
Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val Ser
65 70 75 80

Leu Glu Lys Arg Glu Ala Glu Ala Met Val Leu Gly Ile Gly Pro Val
85 90 95
Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp
100 105 110
Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu
115 120 125
Gly Ile Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala
130 135 140
Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile
145 150 155 160
Leu Gly Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro
165 170 175
Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg
180 185 190
Gln Ala Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu
195 200 205
Gly Tyr Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro
210 215 220
Tyr Leu Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile
225 230 235 240
Phe Leu Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala
245 250 255
Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser
260 265 270
Pro His Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly
275 280 285
Ala Leu Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr
290 295 300
Leu Arg Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met
305 310 315 320
Thr Phe Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln
325 330 335
Gly Val Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp
340 345 350
Glu Gly Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile
355 360 365
Ser Leu Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly
370 375 380
Thr Arg Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala
385 390 395 400
Gly Ala Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala
405 410 415
Ala Leu Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr
420 425 430
Leu Ala Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr
435 440 445
Arg Gly Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser
450 455 460
Phe Leu Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val
465 470 475 480
Gly Ala Gly Gly Ser Gly Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly
485 490 495
Ala Ser Ala Cys Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr
500 505 510
Glu Ala Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile
515 520 525
Leu Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met
530 535 540

```
Gly Ser Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser
545                 550                 555                 560
Ala Ala Gly Leu Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val
                565                 570                 575
Phe Asp Lys Ser Asp Leu Ala Lys Tyr Ser Ala Gly Gly His His His
            580                 585                 590
His His His
        595
```